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PART ONE

# Circulation

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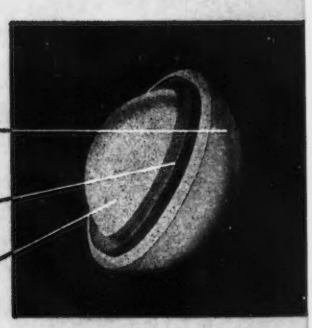

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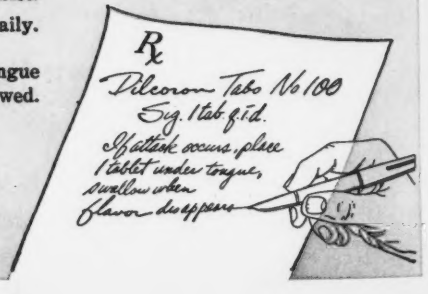


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AN OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

# Editorial

## A Milestone in Cardiovascular Training

THE PUBLISHING of a list of training programs supported by the National Heart Institute (to be found as a separate supplement to this issue) dramatizes the astonishingly rapid increase in research emphasis that has taken place in medical education in recent years. The list of the National Heart Institute programs will, of course, be of particular usefulness to young people planning their professional careers and those who counsel them. But it will also be of great interest to all who are involved in cardiovascular teaching, research, or practice, for it reveals much about the changing methods and emphases in cardiologic training and perhaps, by the same token, foretells the practice of cardiology of the future.

One striking feature of this list is the evidence that, at long last, close collaboration has grown between clinical and preclinical departments in research training. For example, among the programs involving clinical investigation, 15 have formal affiliation with preclinical departments and there are many others in which the collaboration is informal. Evidently the frontier in clinical research is an arena where skill in fundamental sciences is becoming more and more important, and the aspiring researcher and academician feels his clinical competence must be supplemented by solid backing in the preclinical sciences, a backing he evidently did not adequately acquire during his undergraduate years. This emphasis on basic sciences in clinical research will not be news to those who have watched the shift in research technology over the years as reflected in the pages of this journal. But perhaps it will come with surprise to note the 3 training programs in which clinical departments have joined forces with engineering colleges, to bring the technics and disciplines of even the fundamental physical sciences directly into clinical research. Nor will the frequent mention of training in mathematics and physics in the programs escape attention.

This interdepartmental approach to cardiologic training must signal a shift in point of view in the clinical departments of medical schools. Evidently, the leadership among internists, surgeons, and pediatricians in cardiology thinks that a tour through a variety of clinics and an exposure to diagnostic catheterization, electrocardiography, etc., are no longer sufficient background for the cardiologist of the future. If these training programs are representative of a trend, the clinical cardiologist of the future, be he internist, surgeon, or pediatrician, will clearly have a much more solid background in relevant physiology, biochemistry, even biophysics than his seniors now have. This change cannot be other than salutary. Perhaps the distance between cardiovascular research and clinical practice, now so wide for so many of us, will be narrower for these future physicians.

One surmises that these programs joining clinical and fundamental sciences are developed because there is a demand for them. But one cannot help wondering how much demand there is for some of the more ambitious among them. The number of young people adequately equipped to make effective use of such opportunities cannot be large. Possibly one of the most important results of publishing this list will be to inform those who guide young people in their professional careers of these powerful training opportunities, so that the unusually well qualified and strongly motivated aspirant may find a research training opportunity equal to his abilities.

Another noteworthy type of training opportunity represented in this list is in the field of clinical therapeutics. For too long the academic medical community has ignored its responsibility in this regard. Programs that aim to turn out persons skilled in biostatistics and theory of drug action, as well as in clinical investigation, fill an important need, as more and more potent agents are introduced into medical practice by biochemists and the pharmaceutical industry. It is hoped that many young people will see the exciting future that lies in this field of research.

We are told this list is only a part of the training programs supported by the National Heart Institute, and that the training programs supported by other Institutes of the National Institutes of Health and other federal and voluntary sources are not included. With so many opportunities for training, one wonders how many young recent graduates from medical schools are receiving training in medical research. Adding together some of the figures available from various sources, there must be, one hazards, as many as 3,000 young people in medical research training programs this year, perhaps as many as 500 in cardiovascular research training alone. Additional arithmetic leads to the rough conjecture that perhaps as many as 15 to 20 per cent of each annual graduating class of M.D.'s must be entering research training for longer or shorter periods of time. To be sure, for many —perhaps most—it is a pause before, or prelude to, clinical practice. But the figure is impressive, and whatever the destiny of these young people, they cannot other than greatly influence the nature of medical practice—and for the better.

But this trend also raises problems, and we are confident those responsible for these programs are not unmindful of them. What of the capable young man who productively completes his training, and wishes to remain in investigative medicine? Are there adequate opportunities with reasonable economic support for him? The medical schools must recognize their obligation on this score. Perhaps the growing tendency among many larger hospitals and even private medical groups to foster research laboratories in their structures is another answer, serving also the healthy purpose of bringing medical science into community medical practice.

Another problem: how to guide the promising medical student to this type of training and prepare him optimally for it. Most medical schools are actively and creatively attacking this problem, but anterior to this is perhaps an even more urgent problem: how to attract potentially gifted young high school and college students to careers in medicine, especially youngsters with a scientific bent who may, through these research training opportunities, make contributions to medical science. Anxiety has been expressed in several quarters about dwindling numbers and dwindling quality of applicants to medical schools. These problems are, perhaps, more properly the business of other journals and other editors. Nevertheless, none of us can escape responsibility for furthering the growth of scientific medicine in his respective sphere. The editors of *Circulation*, mindful of their responsibility in this regard, are happy to devote some of their pages to making as widely known as possible the research training opportunities that are available in cardiovascular fields.

# Starling and the Concept of Heart Failure

*By* Sir George Pickering, M.A., M.D., F.R.C.P.

ERNEST HENRY STARLING has probably contributed more than any man to our understanding of heart failure. Thus his early experiments on edema formation and his assessment of the factors concerned have formed the basis for all subsequent work on this subject. His work with Patterson and Piper[1, 2] on the mechanical factors involved in the response of the heart to changes in load have formed the basis for our understanding of how the heart's work as a pump is adjusted to the varying demands made upon it, and have incidentally provided the key to our understanding of heart failure as seen in man. Nevertheless, in the course of time what Starling and his colleagues actually observed, and what they deduced from these observations that was relevant to heart failure, have become somewhat obscured. And since it would seem to the writer that Starling's concept of the nature of heart failure was closely in accord with what actually happens in man, it seems right to present some extracts from the original papers so that cardiologists, whether practitioners or investigators, may be more fully informed than they are.

It is to be remembered that Starling was a physiologist, and that though undoubtedly he received much inspiration from human disease, he was more interested in basic mechanism than in the interpretation of morbid phenomena. Hence in his "Linacre Lecture on the Law of the Heart,"[3] and in his text book of physiology, it is the relationship between initial length of muscle fiber and the tension developed during contraction that is the center of his interest. Perhaps it is because modern investigators have been more closely acquainted with these works than with the originals that has led to some of Starling's conclusions, which are most relevant to heart failure, being overlooked.

A paper delivered before the Washington State Heart Association, September 1958.

### Starling's Experiments

Starling's great technical achievement was the heart-lung preparation. In this preparation, while the blood circulated through the animal's lungs in the ordinary way, it passed from the aorta through a cannula in the brachiocephalic artery, through an adjustable resistance, then through a warming coil to the venous reservoir, and back to the heart through a cannula in the superior vena cava. The lungs not only oxygenated the blood, they removed vasoactive substances that had hitherto made difficult perfusion of organs with blood. Moreover, in this preparation right atrial inflow and aortic pressure were controlled, while pressure in the vena cava, and in the aorta, as well as cardiac output, was measured.

The experiments on which the law of the heart were based were the subject of 2 papers, the first by Patterson and Starling,[1] the second by Patterson, Piper, and Starling.[2] In the first paper Patterson and Starling were concerned with the mechanical factors that determined the output of the ventricles. These experiments were prompted by the controversy that had existed up to then as to the extent to which the heart could alter its output, a controversy that was due to the imperfect methods of measuring this in the whole animal. They first investigated the connection between venous inflow, ventricular output, and venous pressure. They wrote:

> If we are to understand the factors responsible for the power of the heart to adapt its output to the inflow, it is necessary to study the relation of the pressures on the venous side of the heart to the volume of inflow. This relation is shown in the curves in which the venous pressures in nine different experiments, as measured on the right side of the heart, are plotted against the output (fig. 1). It will be seen that as the inflow and output gradually increase, there is a slight rise of venous pressure with each increase. The height of the venous pressure does not, however, rise in a straight line but in a curve, becoming

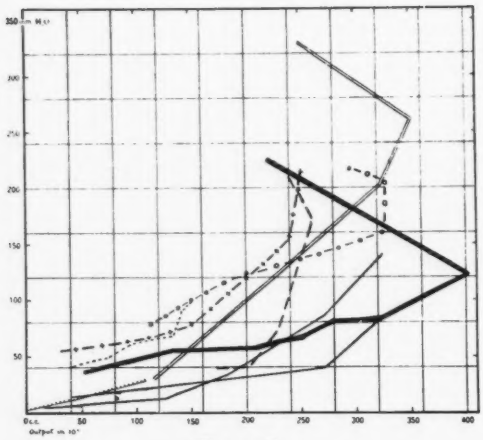

**Figure 1**

*Shows the relationship between venous pressure in mm. $H_2O$ (ordinate) recorded from the cannula inserted into the inferior vena cava and the cardiac output in milliliters per 10 seconds (abscissa) in nine separate experiments in the dog heart-lung preparation. In each experiment the venous inflow was increased either by raising the venous reservoir or altering the size of the clip connecting it to the cannula in the superior vena cava. After Patterson and Starling, J. Physiol.* **48:** *357, 1914. (Figures 1, 2, 3, 4, 6, and 7 are reproduced by courtesy of the authors and the publishers.)*

more rapid as the limits of the functional capacity of the heart are reached, until in some cases the heart becomes over distended, is unable to deal with the blood filling its cavities, and the output diminishes, although the venous pressure rises to a maximum. During the first part of the curve, with small to moderate output, we may say that the venous pressure, as measured at the entry of the vena cava into the right auricle, is mainly important in providing a quick flow of blood into the right auricle and ventricle, so as to maintain a slight distending force on the relaxing ventricle, so that the blood is always present to follow the ventricular wall as it relaxes. As the inflow increases still further, the pressure begins to rise more rapidly and now becomes an effective factor in distending the ventricular wall and quickening the rate at which lengthening occurs after the end of systole. It is evident that there must be some limit to the process by which rise of venous pressure causes increased filling and increased output of the heart. This limit is probably reached when the venous pressure is high enough to produce maximal distension of the heart just as the next systole begins. This explanation, however, at once brings in the further question as to the significance of maximal dilatation. Is the maximum set by the connective tissue framework of the muscular heart wall, or does it vary with the functional capacity of the heart? The fact that with a high arterial resistance the maximum possible output is smaller than with a moderate resistance would at first seem to point to the optimum distension as being dependent on the functional capacity of the heart muscle. We have found, however, that, as the arterial resistance is increased, the amount of residual blood remaining in the ventricle after each systole is also increased, so that, assuming that each heart has a constant maximum distension set by the length of its muscle fibres and the arrangement of its connective tissue, it will attain this maximum during diastole with increasing venous inflow sooner, if the arterial resistance is high, than when the arterial resistance is low. We are inclined therefore to believe that the maximum capacity of the heart is a fixed quantity for each heart and is dependent on its structural arrangements.

The effect of moderate fatigue is well shown in Exp. 2. In this animal, with a heart of 44 gms., an output of 2000 c.c. per minute was obtained at the beginning of the experiment with a venous pressure of 80 mm. $H_2O$ against an arterial pressure of 112 mm. Hg. About half an hour later in the same experiment, with the same rate of beat and the same arterial pressure, the same output of 2000 c.c. per minute was only obtained with a venous pressure of 130 mm. $H_2O$. This experiment shows us what fatigue of the heart means. In the fatigued heart a greater diastolic distension is necessary to produce a given output of blood at each systole than is required in the fresh heart beating at the same rate. This distension can only be produced by increasing the venous pressure.

I would like to emphasize to the reader the importance of this last paragraph. If we substitute in the last 3 sentences "heart in failure" for "fatigued heart," we have clearly displayed a concept of heart failure that tallies closely with what is seen in man. Moreover, if the reader cares to compare the details of the experiment given with figure 1, he will see that the fresh and the fatigued heart are behaving so differently that their behavior would not be expressed by points on the same curve. As figure 1 shows, each curve represents an individual heart, and as experiment 2 illustrates, an individual heart in a partic-

l r state of fitness or tone; when its fitness a ters, the position of the curve alters also.

Patterson and Starling recognized that the l art consisted of 2 pumps and they therefore measured simultaneously the pressure in the l ft atrium with that in the right. With re- g rd to these experiments they say:

> These results show that, in a heart that is in good condition, as the inflow is increased from a minimal to a moderate amount, the pressure in the left auricle rises at approximately the same rate as the pressure on the right side of the heart. This is what we should expect, since increased pressure in the inferior vena cava causes increased filling of the right heart and therefore increased output. The whole of this output is driven into the left auricle, so here again there must be a direct connection between venous pressure, diastolic filling and output. When, however, the demands on the functional capacity of the heart are increased by increasing the inflow into the right side of the heart to a maximum, marked differences may be found between the pressures in the right and left auricles, and these differences are especially pronounced when the heart fails or is on the point of failing. They are due to the fact that failure may commence on one side of the heart before the other, and that as a rule the side on which failure commences will be determined by the stress which is laid on it.

In their conclusions to this paper they wrote:

> With a constant inflow, fatigue of the heart is shown by a rise of venous pressure accompanied by increased diastolic filling and mean volume of the heart, the outflow remaining constant.
>
> The above statements as to venous pressure apply to both sides of the heart. When failure occurs under a maximal load, either the right or the left side of the heart may fail before the other side.

In the second paper of the series they added 2 further technical methods. They placed a cardiometer over the ventricles and were thus able to measure the volume changes with each beat of the heart, and they introduced a manometer into the cardiac cavity so that they could record the changes in pressure during the heart beat. In the course of this long and important paper they showed that when the heart was called on to increase its work because of a sudden increase in the arterial resistance, the stroke volume at first fell so that

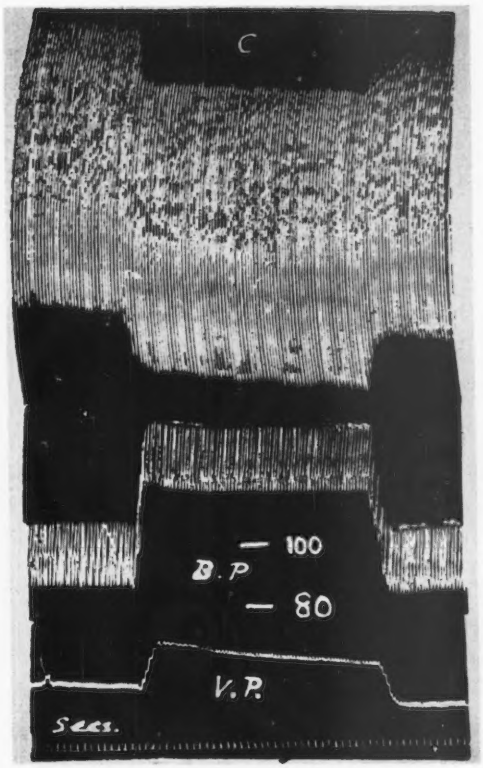


**Figure 2**

*The effect of increased arterial pressure on the volume changes of the heart with a large inflow, 154 ml. per 10 seconds. Heart-lung preparation of the dog. C., cardiometer tracing; increase in volume of the heart represented by downward movement on the tracing. B.P., arterial blood pressure. V.P., venous pressure. The arterial pressure was raised by increasing the resistance in the circuit leading from the aortic cannula. After Patterson, Piper and Starling, J. Physiol.* **48**: *465, 1914.*

the cardiac size rose, until finally at a new and increased diastolic size, the heart was putting out its original output but at a greatly increased pressure (fig. 2). This increase in diastolic size was accompanied by an increase in the venous pressure in the right atrium. Similarly, when the inflow was increased, arterial pressure remaining constant, the heart gradually distended until, at a new and larger diastolic size, it put out a much larger outflow

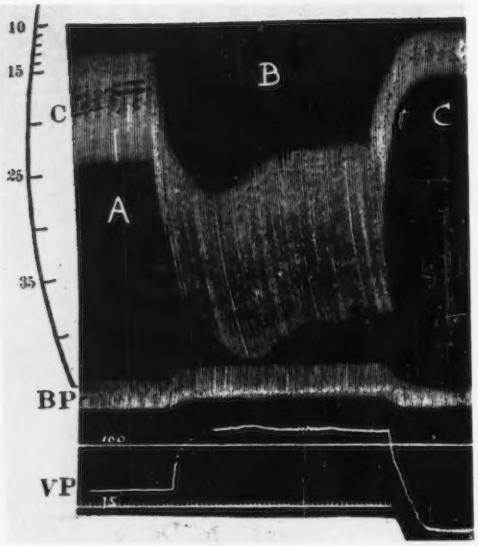


**Figure 3**

*The effect of alterations in venous supply on the volume of the heart. Dog heart-lung preparation. Upper tracing cardiometer; downward deflection represents increased volume. B.P., arterial pressure. V.P., venous pressure. After Patterson, Piper and Starling, J. Physiol.* **48**: *465, 1914.*

than before, this change again being effected through the increased venous pressure (fig. 3). They wrote:

> The law of the heart is therefore the same as that of skeletal muscle, namely that the mechanical energy set free on passage from the resting to the contracted state depends on the area of "chemically active surfaces," i.e., on the length of the muscle fibres. This simple formula serves to "explain" the whole behaviour of the isolated mammalian heart,—its movements, powers of adaptation to varying demands made upon it, behaviour in fatigue and under the influence of its nerves or chemical agencies, such as acid ions or adrenaline.

They sum up the contrast between a heart in good condition and a heart in bad condition as follows:

> It is evident from what we have said above that the word *tone* is properly employed as synonymous with physiological condition or fitness of the muscle fibre, and its measure is the energy set free per unit length of muscle fibre at each contraction of the heart. A good heart, i.e., one with a good tone, will carry on a large circulation against a high arterial pressure and nearly empty itself at each contraction, while a heart with a defective tone, as is the case when it is tired, can carry on the same circulation but only when its fibres at the beginning of contraction are much longer, i.e. when the heart is dilated. In the latter case the output of blood will be the same as in the former, but both the systolic and the diastolic volumes of the heart will be increased.
>
> Fatigue of the heart may go on to heart failure. This occurs when the dilatation, which is the mechanical result of unchanging inflow and failing outflow and is the automatic means of regulating outflow to inflow, proceeds to such an extent that the tension of the muscle fibres becomes increasingly inadequate in producing rise of intracardiac pressure. The mechanical disadvantage, at which in the dilated spherical heart the skein of muscle fibres must act, finally smashes up the system and the circulation comes to an end.

Here again, in this second paper, is a clear concept of what we should now term the various stages of heart failure.

Starling was not a clinician and therefore had no opportunity to interpret his experiments and resultant views in terms of the phenomena seen at the bedside. At that time very few clinicians were in a position to do so, because they knew nothing of the venous pressure. I remember vividly being intern in 1930 to one of the best physicians whom it has been my privilege to know, whose specialty was heart disease, and who was not acquainted with the message contained in the veins of the neck. This struck me most forcibly when I was asked to transfuse a patient with mitral stenosis and severe anemia, whose jugular veins were intensely distended, as the patient sat up in bed. I knew nothing of their meaning except that I had read somewhere that this jugular venous distention was an indication for venesection. It struck me at the time as very odd that a patient who presented a sign indicating the desirability of venesection should be transfused. I was thus in a way scarcely surprised when the patient developed acute pulmonary edema as a result of transfusion and died. It was only when I came to work with Lewis that I first became acquainted with the meaning and importance of estimating the venous pressure from neck veins. Lewis had learned this partly from

Mackenzie, but chiefly from his own use of the polygraph. As he explained to me, if one wants to get a good tracing of the jugular pulse one must apply the venous receiver at a point where distended and collapsed veins meet, that is to say at a point where the venous pressure is approximately atmospheric. He had found that this was commonly beneath the angle of Louis in normal subjects, and above it in those with cardiac failure, and he taught consistently that the venous pressure could be measured by inspecting the veins of the neck and that the height of the venous pressure was the best guide to the presence and severity of cardiac failure. Lewis wrote in *Diseases of the Heart*:[4]

> Study of the veins still suffers an unfortunate neglect; in these vessels are to be found some of the most valuable signs we possess in managing heart cases.

Yet curiously enough I never heard Lewis develop Starling's thesis on the nature of cardiac failure; nor did he develop it in his book. Unfortunately, I never discussed this subject with my old chief. But though Lewis was a great friend of Starling, he was absorbed in mapping the course of the excitation process through the heart at the time Starling was making his important experiments. And I know enough of Lewis's capacity to be absorbed in the problem of the day to suspect that this may be the explanation.

Lewis's ideas partly arose from Mackenzie's views on heart failure. Mackenzie[5] wrote devastatingly against the back-pressure hypothesis and particularly against the practice of seeking the signs of cardiac failure in systolic murmurs that were held to indicate the presence of regurgitation through the atrioventricular valves. Though he never went so far as to state that the symptoms were due to reduced output of the heart, he attributed them to failure of the heart to maintain the circulation. Lewis's views were also much affected by some experiments that he had done with Barcroft, in which he had sent blood from cardiac patients who were breathless to Barcroft, who had determined the position of the oxygen dissociation curve of hemoglobin, and thus the pH of the blood.[6, 7] These experiments convinced Lewis that cardiac breathlessness was due to acidity of the blood, which in turn seemed to him most probably due to diminished cardiac output. Thus, although he recognized that a raised venous pressure was the sine qua non of cardiac failure, and although he attributed this to failure of the heart to transfer blood from the venous to the arterial system, he never really interpreted Starling's experiments in the clinical field.

One of the first clinicians to try to interpret Starling's observations in the light of clinical experience was T. R. Harrison in his book on *Failure of the Circulation*,[8] in which he showed clearly that the hypothesis of forward failure favored by the great masters Mackenzie and Lewis did not explain the phenomena of cardiac failure, which were more consistent with the alternative hypothesis of backward failure. He devoted a good deal of attention to Starling's experiments, and particularly to his law of the heart, but he did quote the passage already described, comparing a heart in good condition with one that was tired. He went on as follows:

> It is well known that an increase in venous pressure almost always accompanies advanced congestive failure, and it will be shown in Chapter 15 that patients with this disorder exhibit on exertion a rise in venous pressure which is unusually marked and unusually prolonged.

However, the modern appreciation of the importance of Starling's experiments to the interpretation of the phenomena of heart failure in man is chiefly due to McMichael and his colleague Sharpey-Schafer. McMichael had worked in Lewis's hospital but was not one of his pupils. Schafer was a pupil of Lewis's. In 1938 McMichael[9] determined the cardiac output by the acetylene method in subjects with the 4 standard grades* of heart failure, both in the erect and supine positions. He showed that in group 1 (without symptoms) the cardiac output and venous pressure were normal, and that there was a considerable rise in cardiac output when the erect was changed to the supine position. This rise he attributed

*American Heart Association classification.

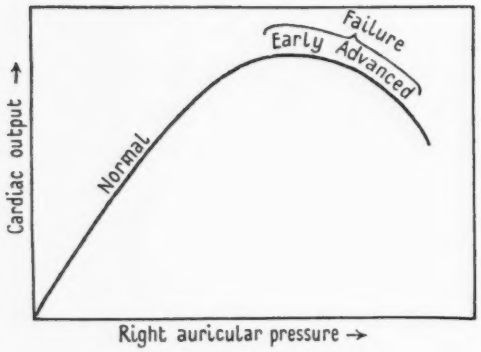


**Figure 4**

*Starling's curve. Increase of filling pressure is accompanied by an increase in output until the heart is overloaded; thereafter the output begins to fall with any further increase in pressure. After McMichael and Sharpey-Schafer, Quart. J. Med.* **37**: *123, 1944.*

to the effect of venous pressure on cardiac output. In group 2b (breathless on slight exertion) cardiac output was slightly subnormal. Venous pressure was slightly raised and there was no change whatsoever in cardiac output on posture. In group 3 (breathless at rest) the cardiac output was reduced, while the venous pressure was grossly raised. Again posture was without effect.

McMichael appreciated the significance of his work in showing that in the early stages of cardiac failure the heart loses its ability to respond to a small change in venous pressure with an increase in output, and in the later stages is working at a high venous pressure. He discussed Starling's views as set out in his Linacre Lecture, his demonstrations of the interrelationship of venous pressure and cardiac output, and Wiggers and Katz's confirmation of it.[10] But he did not relate his results to Patterson and Starling's curve (figure 1) with which they were in close agreement.

McMichael and Sharpey-Schafer in 1944[11] published their results on cardiac output determined with the aid of right atrial catheterization, in which they showed, among other things, that cardiac output in normal subjects was increased by infusion, and reduced by venesection or cuffs on the thighs, and that there was a roughly linear relationship between venous pressure and cardiac output. Later the same year they published results on the action of intravenous Digoxin in man,[12] in which they showed that its most constant action in heart failure was to reduce the greatly elevated venous pressure while usually increasing cardiac output, and that a similar reduction in venous pressure and increase in cardiac output could be obtained by inflating cuffs on the thighs. They attributed the effect of Digoxin to the fall of venous pressure that it produced; they attributed the rise of cardiac output in response to the fall of venous pressure to the heart being "over the top" of Starling's curve, a drawing of which is reproduced in figure 4; and they suggested the possibility that Digoxin might have a primary action on venous pressure, the cardiac response being secondary. These wholly unexpected results naturally caused quite a stir in the world of cardiology. The following year Howarth, McMichael, and Schafer[13] carried their observations further, showing that reducing venous pressure by bleeding in advanced cardiac failure also increased cardiac output. Though further observation on the action of digitalis, particularly in left ventricular failure,[14] has shown that digitalis probably does act through its effect on the heart, the principal observation that in heart failure reduction of venous pressure increases cardiac output still stands. And it clearly parallels in man the phenomenon recorded by Patterson and Starling in the dog's heart.

The similarity between the heart in advanced cardiac failure and the heart at the extreme limits of its performance in Starling's experiments, to which McMichael and Schafer drew attention, naturally excited the greatest interest. The curve which they drew as Starling's curve has been widely accepted as being such. Closer inspection shows, however, that it differs from figure 1 in several particulars. Firstly, it is drawn on its side, a procedure that conforms to modern practice of making the dependent variable the ordinate. Secondly, Starling's curves were not

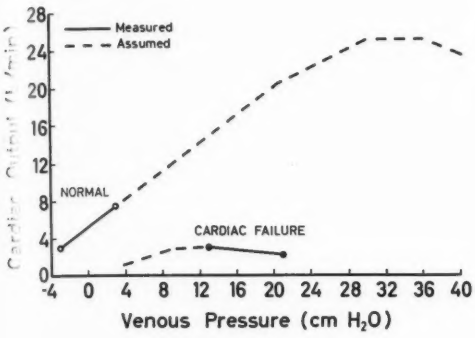


**Figure 5**

*The upper curve shows (continuous line) the line joining 2 points relating venous pressure to cardiac output in a normal subject given an intravenous infusion and venesection;[11] the interrupted line is an imaginative continuation. The lower curve shows 2 points relating venous pressure to cardiac output in a subject with cardiac failure[12] in whom the venous pressure was reduced by cuffs on the limbs; the interrupted line is an imaginative continuation. The imaginative curves are not thought to approximate closely to the truth since, inter alia, small errors in cardiac output will grossly alter the slopes of the lines. But they do illustrate that the behavior of the normal heart and the heart in failure clearly do* not *follow the same curve.*

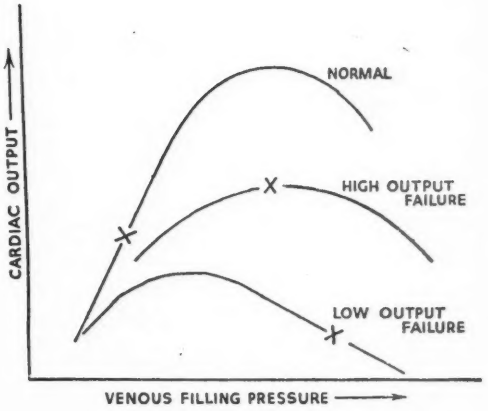


**Figure 6**

*Suggested filling pressure-cardiac output curves for normal subjects and cases of high and low output failure. Crosses represent usual status of each group at rest. After Howarth, McMichael and Sharpey-Schafer, Clin. Sc.* **6**: *41, 1946-48.*

one but several. Thirdly, McMichael and Sharpey-Schafer's curve has no calibration on the ordinate or the abscissa. In fact, if their observations on the relationship between venous pressure and cardiac output in normal subjects and in patients with heart failure are plotted, then it becomes clear that those for the normal heart and those for the heart in cardiac failure must represent very different curves. A figure drawn from their results with the curves completed imaginatively on the Patterson and Starling pattern with the axis reversed is shown in figure 5. McMichael subsequently pointed out that in fact there is a series of curves, and has illustrated his ideas of what they may be (figs. 6 and 7).[13, 15]

A good deal of work has been done on the dog to test the general principles of Starling's work. For example, Sarnoff and Berglund[16] measured atrial, pulmonary artery, and aortic pressures as well as systemic flows in otherwise intact dogs. They showed that the relationship between venous pressure and stroke work of the ventricle was different on the left and the right sides of the heart. They showed that interfering with the nutrition of the heart would alter the shapes of these curves, as would infusions of epinephrine. They go on to say:

> In order to uphold the view of Frank and Starling it has been necessary to broaden this view with a spectrum or family of curves so as to have it encompass the observed phenomena. The idea of a family of Starling curves was first suggested to us by Dow in 1949. In 1952 McMichael drew three theoretical plots of cardiac work against filling pressure representing the normal, the hypodynamic and the hypertrophied heart. The theoretic curves presented by Youmans and Huckins and by Lewis and co-workers unfortunately plotted cardiac output or stroke volume against filling pressure. The data presented above and elsewhere substantially strengthen the view that a ventricle may describe many different ventricular function curves. These data also furnish examples of certain ways in which the curves may be altered.

Similarly, in Harrison's recent text book, Dexter and Harrison state:

> Starling's curve is not a single line but rather a whole family of curves, and the curve for the right ventricle is quite different from that for the left.[17]

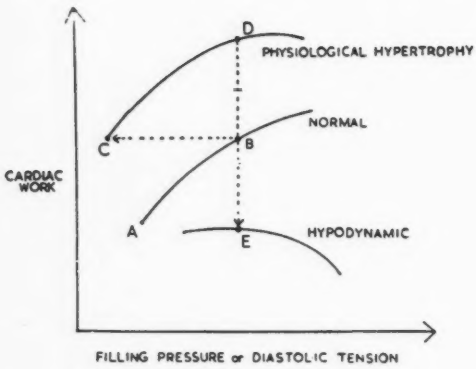


**Figure 7**

*A normal ventricle does work A at a low diastolic tension. Acute load B is accomplished at a higher filling pressure. Development of hypertrophy BC may cope with a chronic load, or the myocardium may be overstrained and become hypodynamic, BE. Hypodynamic state may also develop after physiological hypertrophy, DE. After McMichael, Brit. Med. J.* **2**: *525, 1952.*

If the reader will read carefully the second paragraph quoted from Patterson and Starling's paper he will see that this in fact is what they found. A heart that is fresh and a heart that is "tired" are not on the same curve; they are on different curves. One would also surmise that the effect of digitalis is not to alter the position of the heart on a curve; it is to alter the behavior of the heart in respect to venous pressure and thus to alter the position of the curve relating venous pressure and cardiac output, a curve characteristic for that heart in that state of fitness or "tone," to use the expression common in Starling's time.

Intact man differs considerably from the heart-lung preparation of the dog. The filling pressure of the heart is a compound of the venous pressure and the intrathoracic pressure. Accurate measurements of cardiac output and of the filling pressure of the heart are difficult to make in severe exercise. The diastolic size of the heart is dependent not only on end-diastolic pressure, but on the time over which this pressure has operated. Nevertheless, there seems very little doubt that Starling's curve as shown in figure 1 has only limited application to the normal human heart. The strongest evidence for this is the fact that in exercise, as shown by Liljestrand, Lysholm, and Nylin,[18] the volume of the heart may not be much increased, even though the cardiac output is multiplied many times. Similarly the dog may be exercised to exhaustion without any appreciable rise in venous pressure.[19] Presumably in the intact animal nervous and hormonal effects on the heart alter the contractile powers of its fibers to an extent such that the relationships worked out in the isolated heart no longer apply so simply. In resting man it is disputed whether cardiac output and venous pressure are related. In cardiac failure there is more evidence that the relationship between venous pressure and cardiac output are as depicted in the extreme ends in Patterson and Starling's curves. Moreover there is now evidence to suggest that this part of the curve is due to regurgitation through the atrioventricular valves.[20] Thus the anatomic condition limiting the optimal distention of the heart, which Patterson and Starling correctly surmised in 1914, seems in process of being defined.

It seems a little unfortunate that the idea should have become current that Starling ever thought of a single curve. He stated quite clearly that the difference between a good heart and a bad heart was that, for a given output, the former was working at a low diastolic size and a low venous pressure, the latter at a high diastolic size and a high venous pressure. This would seem to me to be the essence of cardiac failure as we know it in man. Whether the cardiac output is greater than it is in a normal man at rest, as for example in anemia, osteitis deformans, or emphysema, or the cardiac output is less than in a normal man at rest, as for example in rheumatic or hypertensive heart disease, the heart in heart failure is working at a high venous pressure.* In fact I would go so far

*Interestingly enough, in these circumstances, whether cardiac output be high or low, the glomerular filtration rate and the renal plasma flow are both reduced. How this is achieved is now one of the outstanding problems of the day.

as to define cardiac failure in these terms. And as can be seen from the quotations from this paper, Patterson and Starling not only realized for the first time the true nature of heart failure, they clearly saw that the right and left sides of the heart might fail separately, according to the strain that was severally imposed upon them.

In fact, then, Patterson and Starling took us pretty close to interpreting the facts of heart failure in man. When one reflects that this was the work of physiologists, not deeply conversant with heart failure (though Patterson, Starling's son-in-law, is a highly respected physician), and that the object of study was the dog's heart, this ranks as a great achievement, and I think one that has not been appreciated as fully as it deserves.


### Summario in Interlingua

Es discutite, ab le puncto de vista del historia del concepto de disfallimento cardiac, le signification del preparato isolate de corde e pulmon, primo utilisate in studios experimental relative al dynamica del corde del can per le physiologo E. H. Starling, le qual, in collaboration con S. W. Patterson e alteres, publicava su pertinente observationes original in iste campo in duo articulos del anno 1914. Es presentate extense citationes ab iste e altere publicationes de Starling.

Le autor conclude que Starling e Patterson non solmente esseva le primes qui recognosceva le ver natura de disfallimento cardiac, illes etiam videva que le latere dextere e le latere sinistre del corde pote fallir separatemente in dependentia del effortio requirite ab le un o ab le altere de illos.


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# The Use of L-Lysine Monohydrochloride in Combination with Mercurial Diuretics in the Treatment of Refractory Fluid Retention

*By* Albert L. Rubin, M.D., Norton Spritz, M.D., Allen W. Mead, M.D., Richard A. Herrmann, M.D., Warren S. Braveman, M.D., and E. Hugh Luckey, M.D.

IN PATIENTS with fluid retention, a regimen of salt restriction, mercurial agents, and digitalis when indicated usually produces an adequate diuretic response. In many instances, however, these measures become ineffective, and the production of a hyperchloremic acidosis is then necessary to restore responsiveness to a mercurial agent.[1]

Ammonium chloride or calcium chloride, alone or in combination with the carbonic anhydrase inhibiter, acetazoleamide[1, 2] has been used successfully to produce a hyperchloremic acidosis in such subjects. Both salts have an unpleasant taste, however, and often are limited in their usefulness by severe gastrointestinal side effects. Experience in this laboratory now includes 2 instances of hematemesis associated with administration of calcium chloride. Since most patients with resistant edema have decreased liver function, due either to primary liver disease or to congestive liver disease secondary to long-standing heart failure, administration of ammonium chloride may produce ammonia toxicity. Many instances of this complication have been reported.[3, 4]

Because of these undesirable side effects a search was instituted for a more satisfactory source of the chloride ion. At the suggestion of Dr. Vincent duVigneaud the chlorides of the basic amino acids were examined. A child with refractory edema unable to take ammonium or calcium chloride tolerated L-lysine monohydrochloride well, and subsequently had a good diuretic response to mercurial administration.[5] In order further to evaluate the effectiveness of this substance in producing the metabolic effects necessary to reestablish mercurial responsiveness, L-lysine monohydrochloride* was administered to a group of adult patients who had edema resistant to mercurial diuretics. It was found that this material produces an adequate hyperchloremic acidosis without the undesirable side effects of ammonium and calcium chloride.

## Materials and Methods

Fourteen patients received L-lysine monohydrochloride in 16 courses of treatment. Each patient had edema, with or without ascites, due either to Laennec's cirrhosis or chronic congestive heart failure. Patients were selected in whom the primary diagnosis was evident from the history, physical findings, and appropriate laboratory determinations. Preceding the use of L-lysine monohydrochloride, all patients had been hospitalized for a control period, during which a combination of fluid and salt restriction, modified bed rest, digitalis when indicated, and daily mercurial diuretics, often in combination with chlorothiazide, were initially ineffective, or had become so, in producing significant weight loss. In 1 patient, calcium chloride, which had been administered to reestablish responsiveness to a mercurial diuretic, had to be discontinued because of gastrointestinal side effects.

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This work was done during Dr. Rubin's tenure of an Established Investigatorship of the American Heart Association.

*Kindly supplied by the Lysine Division of E. I. du Pont de Nemours and Company, Inc. The product used contains 95 per cent L-lysine monohydrochloride and 5 per cent D-lysine monohydrochloride. This product contains approximately 5 mEq. of chloride ion per gram.

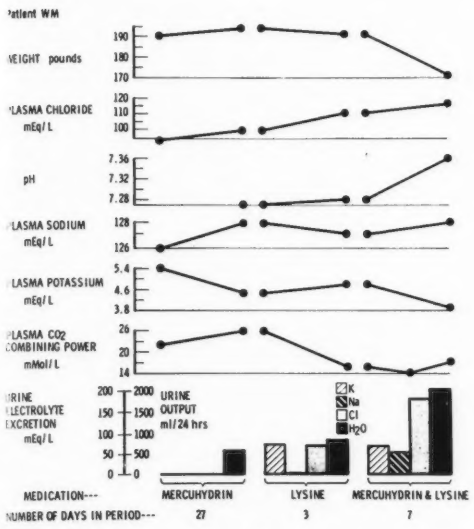


**Figure 1**

*Graphic representation of the data obtained in a patient with Laennec's cirrhosis during the described treatment periods.*

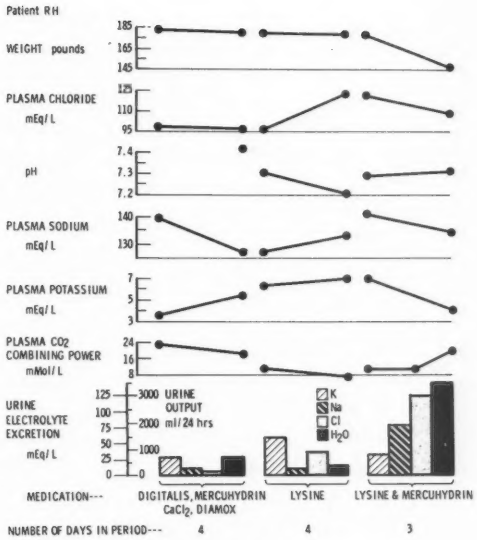


**Figure 2**

*Graphic representation of the data obtained in a patient with congestive heart failure during the described treatment periods.*

L-lysine monohydrochloride was then administered in a dosage of 10 Gm. 4 times a day, usually in fruit juice immediately following a meal. No diuretic agents were administered during this period and no other changes were made in the therapeutic program. Following this preparatory period a daily injection of a mercurial diuretic was given, continuing the same dose of L-lysine monohydrochloride.

Urine volume and body weight were measured daily in all subjects throughout the study. Urine and plasma electrolyte concentrations and blood pH were frequently determined. The methods used for these determinations are described in a previous publication.[1]

## Results

Table 1 is a compilation of the clinical data, electrolyte changes, and response to therapy in each course during 3 phases of observation: (1) the control period preceding administration of L-lysine monohydrochloride; (2) the period of administration of L-lysine monohydrochloride during which hyperchloremic acidosis was produced; (3) the period during which L-lysine monohydrochloride and mercaptomerin were administered together.

Figure 1 is a graphic presentation of the results in a representative subject with cirrhosis of the liver.

### Control Period

The ineffectiveness of the diuretics employed during this period is shown by the constancy of body weight. Patients in whom weight loss is recorded during this period became unresponsive to the diuretics employed and had persistent edema. In patient R. H. calcium chloride was effective in restoring mercurial effect, but had to be discontinued because of nausea and vomiting, and L-lysine monohydrochloride was substituted. Figure 2 records this patient's course.

In those instances in which the initial urine chloride concentration is recorded above 10 mEq./L., a mercurial diuretic had been administered within the preceding 36 hours.

### Production of Hyperchloremic Acidosis with L-lysine Monohydrochloride

Following the control period, the patients were given L-lysine monohydrochloride in dosage of 10 Gm., 4 times daily for 2 to 5 days.

Table 1

*Body Weight, Blood pH, Plasma Carbon Dioxide Combining Power, Plasma, and Urinary Chloride Concentrations in Patients during Various Treatment Periods*

| Diagnosis | Laennec's cirrhosis | | | | | | | | Congestive heart failure | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | W.M. | T.V. | W.T.[1] | W.T.[2] | W.T.[3] | W.F. | H.P. | M.B. | R.H. | E.A. | T.P. | W.C. | C.C. | W.W. | J.R. |
| Control period | | | | | | | | | | | | | | | |
| Number of days | 27 | 27 | 11 | 4 | 19 | 15 | 6 | 6 | 4 | 8 | 8 | 18 | 8 | 10 | 11 |
| Wt. change in lbs. | .25 | 11 | -7 | 2.5 | -2 | -12.5 | -5 | -7.5 | -11 | -.5 | -2.0 | -5.5 | -1.5 | 3 | -1 |
| Urine chloride | 6.4 | 16 | 4.0 | 11.6 | 0.8 | 1.8 | 9 | 2.6 | 2.4 | 17 | — | 12.8 | — | — | 18 |
| Plasma chloride | 105 | 105 | 110 | 113.0 | 106 | 100 | 102 | 104 | 110 | 96 | 104 | — | 111 | 102 | — |
| $CO_2$ comb. power range (mMol./L.) | 22-25 | 27-28 | 29-25 | 19-20 | 27-24 | 30-25 | 14-19 | 34-27 | 23.2 | 24 | 25-23 | 23-19 | 17.4 | 25 | 34-39 |
| Venous pH | 7.24 | 7.36 | 7.46-7.39 | 7.32-7.38 | 7.36-7.40 | — | 7.32 | — | 7.41 | — | 7.31-7.35 | 7.41 | 7.34 | — | 7.33 |
| Lysine alone | | | | | | | | | | | | | | | |
| Number of days | 3 | 2 | 5 | 4 | 4 | 4 | 3 | 3 | 4 | 5 | 5 | 4 | 3 | 3 | 3 |
| Wt. change in lbs. | .5 | 3.5 | -3 | -1.5 | -5 | 0 | 1 | 0 | 0 | .5 | -.5 | -3.0 | -1.5 | 1.5 | -2 |
| Urine chloride range (mEq./L.) | 6-155 | 15-64 | 4.0-110 | 25-146 | 30-147 | 2-107 | 97-135 | 2.6-68 | 2-96 | 25-73 | 11-70 | 17-24 | 76-148 | 56-127 | 18-67 |
| Plasma chloride | 112 | 115 | 120 | 117 | 108 | 107 | 111 | 118 | 122 | 119 | 113 | — | 107 | 107 | — |
| $CO_2$ comb. power range (mMol./L.) | 16 | 27-24 | 24-14 | 20-16 | 25-18 | 30-20 | 19-14 | 27-16 | 23-7.6 | 24-11 | 23-11 | 18-7 | 17-16 | 25-18 | 39-34 |
| Venous pH | 7.29 | 7.23-7.27 | 7.41-7.34 | 7.38-7.29 | 7.42-7.28 | — | 7.26 | — | 7.41-7.20 | — | 7.35-7.18 | 7.39-7.24 | 7.34-7.24 | 7.24 | — |
| Lysine and Mercurial | | | | | | | | | | | | | | | |
| Number of days | 7 | 7 | 6 | 5 | 5 | 7 | 6 | 7 | 3 | 6 | 4 | 3 | 5 | 3 | 5 |
| Wt. change in lbs. | -16 | -13.5 | -18 | -15 | -13.5 | -14 | -16 | -22 | -24 | -8.5 | -32.5 | -28 | -29 | -12.5 | -10 |
| Urine chloride range (mEq./L.) | 217-158 | 250-200 | 176-319 | 216-166 | 83-143 | 107-64 | 155-114 | 68-78 | 137-58 | 73-81 | 128-120 | 127-110 | 148-176 | 140-114 | 67-144 |
| Plasma chloride | 113 | 118 | 116 | 116 | 108 | 104 | 118 | 118 | 114 | 114 | 114 | — | 102 | 109 | — |
| $CO_2$ comb. power range (mMol./L.) | 15-17 | 15-24 | 17-19 | 20-19 | 14-18 | 15-20 | 14-4.5 | 16-26 | 11-19 | 11-22 | 19-14 | 7-17 | 14-17 | 18-15 | 34-35 |
| Venous pH | 7.33-7.36 | 7.27-7.27 | 7.35-7.34 | 7.29-7.25 | 7.28-7.29 | — | 7.27-7.32 | 7.28-7.33 | 7.28-7.32 | — | 7.18-7.19 | 7.29 | 7.34-7.30 | 7.24 | — |

During this period significant weight loss did not occur. In all instances, an increase in plasma chloride concentration and a fall in carbon dioxide combining power (as low as 7.6 mEq./L.) occurred. Blood pH fell in most instances, the lowest recording being 7.18. In no instance was hyperpnea or any other symptom attributable to the acidosis observed.

An increase in the urine chloride concentration to 40 m.Eq./L. or more was a useful indicator that responsiveness to mercurial administration might be expected. This criterion was based on previous studies in this laboratory.[2] In patients who began receiving L-lysine monohydrochloride within 24 hours following an injection of mercurial diuretic, the initial urine chloride often exceeded 40 mEq./L. without a diuresis. In such subjects a further rise of urine chloride concentration of 40 mEq./L. or more was used as the indicator of satisfactory hyperchloremia.

#### Mercurial Administration Following the Production of Hyperchloremic Acidosis

In the setting of the hyperchloremic acidosis produced by the administration of L-lysine monohydrochloride, the administration of a mercurial agent was associated with a significant weight loss in all patients studied.

L-lysine monohydrochloride was continued to maintain the hyperchloremia during mercurial administration. The plasma chloride level returned toward normal during the diuresis. Potassium depletion was prevented by the administration of oral potassium chloride in amounts determined by the magnitude of the diuresis. Usually 3 to 6 Gm. of potassium chloride were sufficient.

In most instances the diuretic program was discontinued because a satisfactory clinical response had been produced. In some patients the therapeutic program became ineffective following an initial response, with significant edema or ascites still present. In several such patients the reestablishment of a hyperchloremic acidosis was associated with further mercurial diuretic response and further weight loss.

#### Side Effects

This chloride salt has now been used in our clinical services for more than 2 years. L-lysine monohydrochloride proved to be acceptable to all patients studied. Cold fruit juice was found to be the most satisfactory vehicle for its administration, and the product was given immediately after a meal whenever possible. In no case was the medication refused—a not uncommon occurrence with both ammonium and calcium chloride. No side effects necessitating the discontinuance of L-lysine monohydrochloride have occurred. There has been no instance of gastrointestinal bleeding associated with its administration.

Diarrhea was the only side effect noted, and it was never severe enough to require discontinuing the L-lysine monohydrochloride. In 1 instance diarrhea that had occurred in one course of treatment did not recur during a second.

Many of the patients had far advanced impairment of liver function at the time of study. In no instance was development of flapping tremor, mental change, or other significant clinical deterioration noted as a result of L-lysine monohydrochloride administration.

Frequent urinalyses and blood urea and hematologic studies revealed no evidence of renal or hematopoietic toxicity.

### Discussion

L-lysine monohydrochloride is a salt of a naturally occurring amino acid with a molecular weight of 195. It has been used in commercial food and vitamin preparations, and no human toxicity has been reported. In animal studies, large amounts of L-lysine monohydrochloride, administered in a setting of specific deficiency of other amino acids, have been associated with interference with optimal growth.[6, 7] The experimental conditions in these animal studies were extreme, and actually have no clinical counterpart in these studies. Five-gram doses of L-lysine monohydrochloride administered to normal adults produced measurable increases in gastric peptic activity without producing gastrointestinal symptoms.[8] It would therefore appear

advisable to insure adequate protein intake in subjects given L-lysine monohydrochloride in the amounts needed for adequate hyperchloremia, and to use caution in patients in whom increased peptic activity represents an added risk. In no instance, however, has activation of peptic ulcer disease or bleeding from esophageal varices occurred. It should be noted that the daily dosages employed in this study were 40 to 80 times as large as the quantities normally employed when L-lysine monohydrochloride is given as a dietary supplement.[9]

In these patients selected on the basis of resistance to usual diuretic regimens, L-lysine monohydrochloride alone, as would be expected, did not produce a diuretic effect in patients with milder degrees of fluid retention; however, it is probable that L-lysine monohydrochloride in smaller doses will be a useful diuretic drug when given alone as well as in association with mercurial diuretics.

The production of a hyperchloremic acidosis by the method described should be reserved for refractory fluid retention states. It must be emphasized that its application requires close clinical observation and frequent pertinent laboratory examinations in order to avoid the potentially serious consequences of a severe metabolic acidosis. It is a program that we believe should be undertaken only in the hospitalized patient.


### Summary

Administration of large doses of L-lysine monohydrochloride at meal times has proved to be an efficient method, free of significant side effects, for the production of a hyperchloremic acidosis to restore responsiveness to mercurial diuretics in cardiac and cirrhotic patients with refractory fluid retention. Results obtained in a group of 14 patients are presented and advantages of L-lysine monohydrochloride over previously available acidifying chloride salts are discussed.



### Acknowledgment

The authors express their appreciation to the following research fellows who assisted in these studies: Burton D. Cohen, M.D., Glenn D. Lubash, M.D., and David Brailovsky, M.D.



### Summario in Interlingua

Le administration de grande doses de monohydrochloruro de L-lysina al tempore del repastos se demonstrate efficace—sin significative effectos lateral—in producer un acidose hyperchloremic pro restaurar le responsivitate a diureticos mercurial del parte de patientes con retention refractori de liquido. Es presentate le resultatos obtenite in un serie de 14 patientes. Le avantages de monohydrochloruro de L-lysina es discutite in comparation con previemente disponibile chloruros acidificatori.


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# Fibrinolysin (Plasmin) Therapy in Acute Deep Thrombophlebitis

## A Controlled Study

*By* KENNETH M. MOSER, M.D., STEPHEN B. SULAVIK, M.D., AND GEORGE C. HAJJAR, M.D.

THE magnitude of the literature dealing with deep thrombophlebitis of the lower extremities and its complications reflects not only the interest that this disorder commands among physicians but also the extensive controversy that it has generated. Controversy surrounds even such fundamental problems as the pathogenesis of venous thromboembolism, the natural course of the process, and the adequacy of available diagnostic criteria.[1-21] When viewed against this background of debate over basic issues, the differences of opinion regarding the effects of various forms of therapy in acute deep venous occlusion are readily understood.

Venous ligation and anticoagulant therapy alone or in combination have attracted strong advocates.[3, 4, 7, 8, 20-22] This debate over therapy is complicated by the variations in the specific manner in which therapy is applied.[4, 17, 20-27]

Furthermore the results can be interpreted only after consideration of the criteria used for selection of patients, the specific measures of improvement, and the therapeutic objectives. Since methodologic details obviously influence the results and since identical methods rarely have been used in evaluation of therapeutic agents in thrombophlebitis, the obvious corollary has been a wide divergence in results.[2]

Recently, a new aspect has been added to this already complex therapeutic problem by the development of agents that are capable of acutely dissolving intravascular clot. Such substances have been categorized broadly as "fibrinolytic or thrombolytic agents," since they can induce the lysis of fibrin, the protein which provides the framework of intravascular thrombi.[28-39]

Materials labeled as "fibrinolytic agents" vary widely in origin, composition, and mechanism of action.[40-42] All of them, however, act by influencing or supplementing the normal components of the intrinsic fibrinolytic mechanism present in the blood (fig. 1).

During the past several years, 3 fibrinolytic agents (streptokinase, fibrinolysin, and the bacterial pyrogens) have been subjected to intensive laboratory and animal testing with encouraging results. While differences among them require further study, preliminary observations have consistently suggested that fibrinolysin, the bacterial pyrogens, and streptokinase are all capable of inducing dissolution of fresh intravascular clot in man.[33, 36, 43-46]

We have previously reported in detail investigations of both the therapeutic effect and the toxicity of highly purified human fibrinolysin administered intravenously in man.[30, 31, 43, 44] These studies indicated that this preparation (a highly purified profibrinolysin activated with streptokinase and then further purified) was acceptable for use in human subjects although it was not devoid of side effects, particularly pyrogenicity. Furthermore, this agent appeared to influence favorably the course of peripheral arterial

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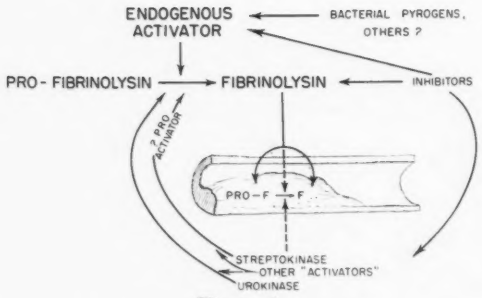


**Figure 1**

*Diagrammatic representation of the normal fibrinolytic mechanism and the influence of various "fibrinolytic agents" upon it.*

and venous thrombotic disorders. Carefully controlled studies were necessary, however, to confirm these preliminary impressions of the therapeutic value of fibrinolysin.

The first entity chosen for controlled investigation was acute deep venous thrombosis of the lower extremities. This particular thrombotic disorder was selected for several reasons: (1) it is encountered frequently at the institutions cooperating in this study; (2) any temperature elevation occasioned by fibrinolysin would be unlikely to have deleterious effects upon these patients; (3) the mortality associated with thrombophlebitis is low and would grant an opportunity for follow-up in most instances; (4) some objective criteria exist for determining the therapeutic effect of a given regimen; and (5) the available methods of therapy are not ideal.

In regard to this last point, the ideal therapeutic regimen in patients with acute deep venous occlusion would achieve 4 major goals: the rapid relief of acute signs and symptoms with early return of the patient to normal activity; the prevention of pulmonary embolism; the prevention of permanent residuals such as the postphlebitic syndrome; and the prevention of phlebitic recurrence.

The study reported here is an attempt to ascertain whether a combined fibrinolytic-anticoagulant therapy attains these 4 objectives more adequately than anticoagulant therapy alone. The data presented are derived from the first 62 patients studied.

## Methods of Study

### Fibrinolysin

The fibrinolysin preparation used in this study* is derived from the euglobulin fraction of the human plasma proteins as pro-fibrinolysin and is activated by small amounts of highly purified streptokinase. Procedures are then employed to obtain an end-product free of detectable streptokinase activity and the material is lyophilized. The precise methods used in isolation, purification, and activation of the material are not available for publication. Studies in our laboratory with the fibrin plate methods of Astrup and Mullertz[47] and Lassen[48] have indicated that the material contains both "activator" and "enzyme" activity. The preparation is standardized by the manufacturer by both fibrinolytic and nonfibrinolytic technics. In our laboratory, the potency of each lot received is compared with a house standard by a fibrinolytic assay method.[31] The lyophilized material is stable for many weeks at 5 C. It is dissolved in normal saline or 5 per cent dextrose solution just prior to use.

### Criteria for Inclusion of Patients

The patients in this series include all individuals seen by the authors during a 2-year period in whom unequivocal signs of acute deep venous occlusion of the legs had been present for 10 days or less. All patients with questionable or minimal evidence of occlusion, complicating cellulitis, or mild exacerbation of chronic venous disease were excluded.

The double-blind technic of study was not feasible in this series because of (1) the pyrogenicity of the fibrinolysin preparation and (2) the desire to obtain serial blood samples and other data (electrocardiogram, temperature response, etc.) in those receiving fibrinolytic therapy. Therefore, an alternating technic of controlled study was employed. Each patient was assigned a number in sequence. All even-numbered patients served as controls while all odd-numbered patients received fibrinolytic therapy. No deviation from this sequential assignment was permitted, with 1 exception; namely, in patients who had received anticoagulant therapy for more than 24 hours prior to their referral. The following arbitrary procedure was followed when such patients were encountered: (1) if the protocol for the study had not been followed or adequate records were not available regarding initial and subsequent status of the leg, the patient was eliminated from the series; (2) if the first criterion was satisfied, the patient was assigned a sequential number. If this was an even (control) number, the patient was continued in

*Supplied as *Actase*—fibrinolysin (human) by the Ortho Research Foundation, Raritan, N.J.

this category. If the patient was to be a fibrinolysin case, the patient was reassigned to the control group if significant improvement had occurred prior to the time of referral. Such breaks in sequence were necessary in only 5 instances, since referrals in the early stages of the study usually were made because of failure of response to therapy and, as the study progressed, patients were usually seen within the first hospital day.

### Therapy

The therapeutic protocol in the control group was as follows: 1. As soon as the diagnosis of thrombophlebitis was established, the patient was placed at bed rest with the legs elevated. Heparin was begun in a dosage of 75 to 100 mg. subcutaneously every 6 hours. Bishydroxycoumarin or warfarin was usually administered simultaneously, but heparin was continued until the patient had remained in a 1-stage prothrombin time range[50] of 10 to 30 per cent for at least 24 hours.

2. The patient was permitted to ambulate with elastic bandages approximately 48 hours after the acute phlebitic signs had subsided (i.e., fever; heat, redness, tenderness and turgidity of the extremity). Slight residual edema or increased size of the extremity was not considered a contraindication to ambulation.

3. After 1 full day of uneventful ambulation, anticoagulant therapy was tapered, and it was discontinued within the next 36 hours.

4. The patient was observed for 24 to 48 hours after cessation of anticoagulant therapy and discharged.

5. With recurrence of phlebitic signs or symptoms, the therapeutic regimen was reinstituted. If pulmonary embolization occurred, the patient was kept in bed and on anticoagulant drugs as long as dyspnea, chest pain, temperature elevation, tachycardia, or electrocardiographic abnormalities persisted and the protocol was again followed regarding ambulation, discontinuation of anticoagulant therapy, and discharge.

Exactly the same therapeutic regimen was used in the group treated with fibrinolysin, with the exception that these patients received an intravenous infusion containing 75 to 100,000 units of fibrinolysin over a 3- to 4-hour period as soon as they had been evaluated. The following day, if significant signs or symptoms of phlebitic activity persisted, the patient received a second dose of 50 to 75,000 units over 2 to 3 hours. Thereafter, regardless of response, no further fibrinolysin was administered. Ten patients received 2 infusions; the remainder, 1. Drugs were used to prevent or ameliorate febrile response in most patients and included aspirin, antihistaminics, or barbiturates.

**Table 1**

*Location of Phlebitis*

| | Fibrinolysin | Control |
|---|---|---|
| Popliteal | 13 | 16 |
| Femoral | 8 | 6 |
| Iliofemoral | 11 | 8 |
| | 32 | 30 |

### Parameters Studied

The following features of the patient's course were documented as accurately as possible: onset of phlebitic signs and symptoms; duration of bed rest and anticoagulant therapy; complications of fibrinolytic or anticoagulant therapy; disappearance of turgidity, edema, pain, and tenderness in the involved extremity; date of return of leg size to normal; date of ambulation; date of discharge; pulmonary embolization or phlebitic recurrence; the presence of postphlebitic changes following the acute episode; possible etiologic factors; and location of phlebitic process. The authors personally made daily observations in the great majority of the patients as long as signs or symptoms of thrombophlebitis persisted and also saw virtually all patients in whom either an embolic event or phlebitic recurrence was suspected. The attending physicians were alerted to record daily the status of signs and symptoms throughout the patient's hospital stay. An attempt was made to follow all patients at regular intervals after discharge.

## Comparability of Groups

While strict comparability is virtually impossible to attain in a clinical study of this type, the 30 control and 32 fibrinolysin-treated patients appear sufficiently similar to permit valid conclusions regarding differences in therapeutic response.

### Age and Sex

The mean age of the patients in the control group was 48 years (median 46) and in the fibrinolysin group, 45 years (median 46). There were 16 males in the control group and 15 in the fibrinolysin group.

### Location of the Phlebitic Process

The location of the thrombotic process (table 1) was defined as follows: (1) popliteal: signs and symptoms limited to the popliteal space and distally; (2) femoral: definite involvement of the thigh as well as below the

**Table 2**

*Associated Disorders*

| | Fibrinolysin | Controls |
|---|---|---|
| No obvious cause | 6 | 4 |
| Postoperative | 4 | 4 |
| Prior thrombophlebitis | 10 | 5 |
| Varicosities | 4 | 3 |
| Trauma | 3 | 3 |
| Congestive heart failure | 2 | 3 |
| Debility-dehydration | 3 | 2 |
| Venous catheter | 2 | 2 |
| Pregnancy | 1 | 3 |
| Postpartum | 3 | 0 |
| Miscellaneous | 2 | 6 |
| | 40* | 35* |

*More than 1 factor was present in some patients.

knee; (3) iliofemoral: pain, tenderness, swelling, and turgidity in the inguinal region and thigh as well as below the knee.

### Etiology or Associated Factors

The factors associated with thrombophlebitis in a given patient may have a definite bearing upon the speed of recovery, tendency toward recurrence, and incidence of embolization (table 2). There were no striking differences between the 2 groups.

### Duration before Therapy

The average duration of signs and symptoms of venous occlusion before institution of anticoagulant therapy was similar in the control and fibrinolysin groups (table 3). However, fibrinolysin was administered on an average of 4.3 days after onset of symptoms, representing an average "lag" period of 1.4 days between institution of anticoagulant drugs and fibrinolysin infusion. This "lag" probably represents a penalty in favor of the control group, since, as mentioned above, no patient who was on anticoagulant drugs when first seen was included in the fibrinolysin group if significant improvement had occurred, but all calculations are dated from the start of anticoagulant therapy.

## Results

Prior studies indicated that analysis of the data should take into account 2 important factors: (1) the duration of signs and symptoms prior to institution of control or fibrinolytic therapy and (2) uncontrollable deviations from the protocol regarding duration of anticoagulant therapy, time of ambulation, or time of discharge. In addition, the inclusion of fibrinolysin-treated patients who received anticoagulant drugs for more than 24 hours before fibrinolysin was administered might penalize this group, since the duration of signs and symptoms was dated from the start of *anticoagulant* therapy.

In order to evaluate these factors results have been analyzed in several ways: 1. The "gross" results in both groups are reported; i.e., the *actual* duration of anticoagulant therapy, duration before ambulation was permissible, etc. In addition, in order to eliminate the distortion of gross results due to uncontrollable factors (other disorders present, physician preference, missed orders, etc.), "arbitrary" results for duration of anticoagulation, bed rest, and hospital stay are also presented. These "arbitrary" results were derived as follows: the day on which all signs

**Table 3**

*Course of Phlebitic Episode in Total Groups (72 fibrinolysin, 30 control patients)*

| Duration in Days of | Fibrinolysin Mean (S.E.)† | Control Mean (S.E.)† | P‡ |
|---|---|---|---|
| Phlebitis before anticoagulant therapy | 2.9 (0.40) | 2.8 (0.48) | > .10 |
| Pain or tenderness* | 4.6 (0.43) | 8.1 (1.20) | < .01 |
| Edema* | 4.6 (0.47) | 6.9 (1.10) | < .10 |
| Abnormality in leg size* | 4.8 (0.58) | 7.2 (1.20) | < .10 |
| *Bed rest** | | | |
| Actual | 7.7 (0.32) | 10.8 (1.60) | < .05 |
| Arbitrary | 6.9 (0.48) | 9.3 (0.62) | < .05 |
| *Anticoagulant therapy** | | | |
| Actual | 9.1 (0.74) | 13.6 (1.98) | < .01 |
| Arbitrary | 8.6 (0.50) | 11.3 (0.64) | < .02 |
| *Hospital stay** | | | |
| Actual | 14.8 (1.70) | 19.4 (1.42) | < .02 |
| Arbitrary | 10.6 (0.50) | 13.4 (0.64) | < .02 |

*Reported as days after start of anticoagulant therapy.

†Standard error of the mean.

‡Level of significance of these differences by the *t* test; adjusted where necessary for inequality of group variances.

of symptoms of active phlebitis (pain, tenderness, turgidity, heat of the extremity, and systemic temperature elevation) had subsided was taken as the starting point. In keeping with the protocol "arbitrary" ambulation represents this figure plus 2 days; "arbitrary" discontinuance of anticoagulant drugs, this figure plus 4 days; "arbitrary" discharge, this figure plus 6 days. Thus, if a patient's phlebitis was inactive on day 3 after start of anticoagulant drugs, he "arbitrarily" would be ambulated on day 5, have anticoagulants discontinued on day 7, and be discharged on day 9.

2. Patients from the 2 groups who met the following criteria were selected for separate analysis: all control patients in whom anticoagulant therapy was begun 5 days or less after onset of symptoms (26 patients); all patients treated with fibrinolysin within 5 days after onset of symptoms and within 24 hours after anticoagulant therapy was instituted (21 patients). Again, both "actual" and "arbitrary" values are reported for duration of anticoagulation, bed rest, and hospital stay.

3. In both the subgroups and total groups, "short-term" and "long-term" results are analyzed separately. The former category includes the response of the involved extremity, the incidence of embolization or recurrence of phlebitis during the first 2 weeks following institution of therapy (or until discharge if the patient was discharged before this time and not seen subsequently), and the status of the extremity at the time of hospital discharge. "Long-term" results include any recurrence of phlebitis or pulmonary emboli that appeared more than 2 weeks after start of anticoagulant therapy. With rare exceptions these represent results in individuals no longer receiving anticoagulant drugs.

We should emphasize that the time intervals reported here are dated *from the start of anticoagulant therapy*, not from the onset of symptoms, admission, or administration of fibrinolysin. Therefore, day zero is the day on which anticoagulant therapy (heparin) was started.

**Total Group, Short-Term Results (Tables 3 and 4)**

*Subsidence of Pain and Tenderness*

Pain and tenderness were considered to be absent when the Homans' sign and the Lowenberg test[51] were negative, and squeezing or vigorous palpation of the involved areas did not cause discomfort. These are rather stringent criteria, since patients often report they are pain-free while such maneuvers continue to elicit pain. In the control group, pain persisted longer after start of anticoagulant therapy than in the fibrinolysin group.

*Edema*

Edema was defined as absent when all pitting edema had subsided.

*Leg Size Normal*

Calf measurements were made at 10-cm. intervals above the lower border of the internal malleolus. The thigh was measured at 10-cm. intervals above the tibial tubercle. The involved extremity was considered to have returned to normal size when no circumference was more than 2.0 cm. greater than the uninvolved leg.[52] In 3 control patients and 3 patients receiving fibrinolysin, leg size failed to return to normal during hospitalization. There was no significant difference in the remainder of the 2 groups in this time.

*Bed Rest*

Bed rest was longer in the control group than in the fibrinolysin group. Two patients in the control group who died while still at bed rest were excluded from analysis.

*Duration of Anticoagulant Therapy*

The duration of anticoagulant therapy was longer in the control group than in the fibrinolysin group. Two patients were excluded in whom anticoagulant drugs were continued indefinitely for reasons other than thrombophlebitis.

*Duration of Hospital Stay*

The duration of hospital stay after start of therapy for thrombophlebitis was also longer in the controls than in those treated with fibrinolysin.

**Table 4**

*Short-Term Complications in Total Groups*

| | Fibrinolysin | Control |
|---|---|---|
| Number of patients | 32 | 30 |
| Pulmonary emboli | | |
| Definite, nonfatal | 0 | 3 |
| Possible, nonfatal | 1 | 0 |
| Possible, fatal | 0 | 1 |
| Total | 1 (3%) | 4 (13%) |
| Recurrence of phlebitis | 0 | 2 |
| Postphlebitic residual | | |
| No prior venous disease | 2/21 (10%) | 3/23 (14%) |
| Prior venous disease with no residual | 0/7 | 1/5 |
| Prior venous disease with residual | 3/3 | 0 |
| Total | 5/31 | 4/28 |
| Deaths | 1 (3%) | 1 (3%) |

*Pulmonary Embolization*

Seven control patients (23 per cent) had a history of pulmonary embolization within the 2-week period *prior* to institution of anticoagulant therapy and a questionable embolic event had occurred in 3 others. In the fibrinolysin group, 9 patients (28 per cent) had suffered a pulmonary embolus during the 2-week period prior to start of anticoagulant drugs.

During the 2 weeks following start of anticoagulant therapy, 3 control patients (10 per cent) had definite evidence of nonfatal pulmonary embolization. One additional control patient suddenly developed tachypnea, cyanosis, and shock on the eighth day of therapy and died. Permission for autopsy was denied and this patient is listed as a "possible" embolus.

In the fibrinolysin group, 1 patient developed aching left chest pain some 5 hours after fibrinolysin infusion. Tachypnea, tachycardia, electrocardiographic and x-ray changes were absent. This "possible" embolus was the only one encountered in the treatment group.

*Postphlebitic Syndrome*

Patients were classified as having the postphlebitic syndrome at the time of hospital discharge if they showed evidence of deep venous insufficiency such as edema (either persistent or developing only after ambulation), continued abnormality in leg size, dilatation of superficial veins, or aching in the extremity after ambulation. A number of patients had a history of prior venous disease. Since this may have influenced the extent of residual venous disease, these patients are considered separately (table 4).

In the control group, there were 25 patients who had no antecedent history of venous disease. Two of these died prior to discharge. Of the remaining 23, 3 (14 per cent) had postphlebitic residuals at discharge. Two of these were marked and followed iliofemoral thrombophlebitis. The third was of moderate degree and followed a femoral occlusion. Five control patients, all of whom denied prior residual disability, had a history of venous disease. One of these 5 had moderate chronic venous insufficiency at discharge.

In the fibrinolysin-treated group, there were 22 patients with no antecedent history of venous disease. One of these died prior to discharge. Of the remaining 21, 2 (10 per cent) showed evidence of venous insufficiency at the time of discharge. In one, this evidence consisted of a 2.5-cm. discrepancy in leg size that persisted during a 3-week period after a left iliofemoral occlusion. No edema on ambulation or other signs or symptoms were present. The second patient was discharged with slight edema following a popliteal thrombosis. However, pretibial and pedal edema developed after moderate periods of ambulation. Ten fibrinolysin-treated patients had a previous history of venous disease. Three of these had well-documented, prior postphlebitic defects. Evidence of chronic venous insufficiency at discharge was limited to these 3 patients. As far as could be ascertained, the degree of insufficiency increased in 1 patient and had remained unchanged in the other 2.

*Recurrence of Phlebitis*

In the control group, 2 recurrences appeared within the 2 weeks after therapy was begun, on the twelfth and fifth days. Both patients were ambulatory at the time of recurrence, and one was still on anticoagulant therapy.

**Table 5**

*Duration of Follow-up in Total Groups*

| | Fibrinolysin | Control |
|---|---|---|
| 1 weeks | 7 | 6 |
| 2-4 weeks | 8 | 8 |
| 5-12 weeks | 7 | 6 |
| 13-24 weeks | 5 | 5 |
| 25-51 weeks | 3 | 2 |
| 52 weeks | 2 | 3 |
| | 32 | 30 |
| Mean | 12.3 weeks | 16.3 weeks |
| Median | 6.0 weeks | 6.0 weeks |

**Table 6**

*Long-Term Complications in Total Groups*

| | Fibrinolysin | Controls |
|---|---|---|
| Patients followed more than 2 weeks | 25 | 24 |
| Pulmonary emboli | | |
| Definite, nonfatal | 2 | (2)* |
| Definite, fatal | 0 | 3 |
| Possible, fatal | 0 | 1 |
| Total | 2 (8%) | 4 (17%) |
| Phlebitic recurrence | 3† (12%) | 4‡ (17%) |
| Deaths | 1 (4%) | 4 (17%) |

*Patients included under Definite, fatal.
†Recurrence in opposite leg in 1 patient.
‡Multiple in 1 of these 4 patients.

In the fibrinolysin-treated group, no recurrences appeared during this 2-week interval.

*Deaths*

One "short-term" death was encountered in each group. As mentioned above, the death in the control group occurred suddenly on the eighth day of anticoagulant therapy, presumably due to a pulmonary embolus. The fibrinolysin-treated patient had chronic azotemia and died of progressive uremia 6 days after therapy. The right femoral thrombophlebitis had cleared completely within 3 days. Autopsy revealed a patent left femoral vein and no evidence of pulmonary embolization. Both kidneys were severely hydronephrotic and virtually replaced by masses of renal calculi.

**Total Group, Long-Term Results**

The long-term results (after the initial 2-week period) obviously are influenced by the extent of follow-up in the 2 groups. The median duration of follow-up in the 2 groups is the same, whereas the average duration is longer in the controls than in those treated with fibrinolysin (table 5).

*Pulmonary Embolization*

Of the 24 control patients followed more than 2 weeks, 4 (17 per cent) had one or more episodes of pulmonary embolization (table 6). One of these patients, who had suffered an embolus on the fifth day of anticoagulant therapy, had a second nonfatal pulmonary embolic event 9 months later. She died 3 months later with a third embolic event and congestive heart failure. Permission for postmortem examination was denied. The second patient also had had an embolus during the initial 2-week period. She had several subsequent pulmonary emboli while on anticoagulant therapy, developed intractable cardiac failure, and died 5 weeks after anticoagulant therapy was begun. Autopsy revealed biventricular hypertrophy and dilatation, multiple emboli of varying ages throughout both lungs, and an extensive right iliofemoral venous thrombosis. The third patient, who had recovered uneventfully from her phlebitic episode, entered 10 weeks later with a recurrent phlebitis, evidence of pulmonary embolization, and congestive failure. She died suddenly 7 days after admission. Autopsy showed multiple pulmonary infarctions. The fourth patient was readmitted 8 weeks after the original phlebitic episode with a recurrence of phlebitis, fever, and severe tachypnea. Positive blood cultures and recurrent episodes of embolization characterized his hospital course of 5 weeks. Autopsy revealed thrombosis of the left iliofemoral vein, septic thrombosis of the portal vein, and septic emboli in the liver and lung.

In the fibrinolysin group, 25 patients have been followed more than 2 weeks after onset of anticoagulant therapy. Two patients (8.0 per cent) had nonfatal episodes of pulmonary embolization during the follow-up period—at

**Table 7**

*Course of Phlebitic Episode in "Early Treatment" Subgroups (21 fibrinolysin, 26 control patients)*

| Duration in Days of | Fibrinolysin Mean (S.E.)† | Control Mean (S.E.)† | $p$‡ |
|---|---|---|---|
| Phlebitis before anticoagulant therapy | 2.7 (0.36) | 2.1 (0.45) | >.10 |
| Pain or tenderness* | 3.7 (0.33) | 8.0 (1.31) | <.01 |
| Edema* | 3.5 (0.44) | 7.0 (1.32) | <.02 |
| Abnormality in leg size* | 3.6 (0.63) | 7.4 (1.44) | <.02 |
| *Bed rest** | | | |
| Actual | 6.2 (0.78) | 10.3 (1.76) | <.02 |
| Arbitrary | 5.7 (0.46) | 9.0 (0.66) | <.01 |
| *Anticoagulant therapy** | | | |
| Actual | 8.6 (0.94) | 12.2 (0.65) | <.01 |
| Arbitrary | 7.4 (0.47) | 11.0 (0.92) | <.01 |
| *Hospital stay** | | | |
| Actual | 14.4 (2.24) | 17.4 (2.77) | <.20 |
| Arbitrary | 9.5 (0.47) | 13.2 (0.69) | <.01 |

*Reported as days after start of anticoagulant therapy.

†Standard error of the mean.

‡Level of significance of these differences by the $t$ test; adjusted where necessary for inequality of group variances.

3 weeks and 9 weeks, respectively. The former was associated with a phlebitic recurrence. The latter occurred in a patient who had had multiple episodes of venous thrombosis over the prior 2 months and at autopsy was proved to have carcinoma of the pancreas.

*Recurrence of Phlebitis*

Of the 24 control patients followed for more than 2 weeks, 6 recurrences appeared in 4 patients. One patient developed a recurrence at 17 days with uneventful recovery. In another, recurrence appeared during the third month of follow-up and the patient succumbed to septicemia and pulmonary embolization. The third patient had a recurrence at 1 month and died 6 weeks later with pulmonary embolization and congestive heart failure. The fourth patient had recurrences at 1, 2, and 3 months after discharge but for the subsequent 6 months she had no further complaints other than severe postphlebitic changes of the involved extremity.

In the 25 fibrinolysin patients followed more than 2 weeks, 3 recurrences were observed. One developed 26 days after discharge and was associated with a large, nonfatal pulmonary embolus. Following this admission, the patient had a definite postphlebitic residual. The second patient had a recurrence 10 weeks after discharge and also had chronic venous insufficiency following this episode. The third recurrence was the only one in the opposite extremity in the entire series. This patient had definite persisting abnormalities after the recurrence. The third patient was retreated with fibrinolysin plus anticoagulants; the others, with anticoagulant drugs alone.

*Deaths*

Four "long-term" deaths (17 per cent) have occurred in the control group during the total period of observation. Recent pulmonary embolism at least contributed to death in all 4, being confirmed at autopsy in 3 and evident clinically in the fourth. In the fibrinolysin group, one "long-term" death is known to have occurred. This patient died of metastatic pancreatic carcinoma 8 months after discharge.

**Short and Long-Term Results in Subgroups**

In this section, we have compared the 26 control subjects who were started on anticoagulant therapy within 5 days of onset of signs and symptoms with the 21 fibrinolysin patients to whom fibrinolysin was administered within 5 days of onset and within less than 24 hours after anticoagulant drugs were begun (tables 7 to 9).

*Composition of Groups*

The mean age of control patients was 46.0 years (median 42) versus 49.1 years (median 48) in the fibrinolysin patients. There were 11 men in the control group and 12 in the fibrinolysin group. Duration prior to anticoagulant therapy was 2.1 days in the control group and 2.7 days in the fibrinolysin patients. Location of the phlebitic process remained comparable, as did etiologic factors.

The durations of pain, edema, abnormal leg size, bed rest, anticoagulant therapy, and hospital stay were all shorter in the fibrinolysin-treated than in the control patients (table 7).

**Table 8**

*Short-Term Complications in "Early Treatment" Subgroups*

| | Fibrinolysin | Control |
|---|---|---|
| Patients | 21 | 26 |
| Pulmonary emboli | | |
| Definite, nonfatal | 0 | 2 |
| Possible, nonfatal | 0 | 0 |
| Possible, fatal | 0 | 1 |
| Total | 0 | 3 (12%) |
| Phlebitic recurrence | 0 | 2 |
| Postphlebitic | | |
| No prior venous disease | 2/17 (12%) | 3/22 (14%) |
| Prior venous disease with no residual | 0/2 | 1/4 |
| Prior venous disease with residual | 2/2 | 0 |
| Total | 4/21 | 4/26 |
| Deaths | 1 (5%) | 1 (4%) |

*Pulmonary Embolization*

Of the 26 control patients, 5 (19 per cent) had a history of pulmonary embolism during the 2 weeks prior to start of therapy. Two had nonfatal embolic episodes within the first 2 weeks of therapy and another died suddenly with a "possible" embolus. Follow-up beyond 2 weeks was available in 18 control patients. Of these, 3 had subsequent embolic episodes.

Of the 21 fibrinolysin patients, 5 (24 per cent) had had embolic episodes in the 2 weeks prior to start of therapy. During the first 2 weeks after therapy, no emboli occurred. Sixteen patients in this group were followed more than 2 weeks. Two of these patients suffered nonfatal emboli at 3 and 9 weeks after discharge.

Again the figures on embolic incidence may be weighted by the somewhat greater duration of follow-up in the controls, which averaged 5.7 weeks (median 4) versus 9.1 weeks (median 4) in the fibrinolysin patients. That the recurrence of embolization (or recurrence) leading to hospitalization may have conditioned the better follow-up in the control group, however, must also be considered.

**Table 9**

*Long-Term Complications in "Early Treatment" Subgroups*

| | Fibrinolysin | Control |
|---|---|---|
| Number of Patients | 16 | 18 |
| Pulmonary Emboli | | |
| Definite, nonfatal | 2 | (1)* |
| Definite, fatal | 0 | 2 |
| Possible, fatal | 0 | 1 |
| Total | 2 (13%) | 3 (17%) |
| Phlebitic recurrence | 3† (19%) | 4‡ (22%) |
| Death | 1 (6%) | 3 (17%) |

*Patient included under Definite, fatal.

†One recurrence in opposite leg.

‡Multiple in one patient.

*Postphlebitic Syndrome*

Four patients in the control group (15 per cent) were left with chronic postphlebitic changes at the time of discharge, including one with a history of prior venous disease that had left no residual. Four fibrinolysin patients (19 per cent) had postphlebitic changes at discharge. Two of these had no antecedent venous disease, while 2 had residuals from prior venous occlusion.

*Recurrence*

Two "early" recurrences appeared in the 26 control patients versus none in the fibrinolysin group. Six "late" recurrences appeared in 4 of the 18 control patients followed for more than 2 weeks (22 per cent) versus 3 recurrences in 3 of the 16 fibrinolysin patients.

*Deaths*

One "short-term" death occurred in each group. Pulmonary embolism was the probable cause in the control patient and uremia in the fibrinolysin patient. Of the 3 "long-term" deaths in the control series, 2 were due to pulmonary embolism and embolization contributed to death in the third. The one "long-term" fibrinolysin death resulted from metastatic carcinoma of the pancreas.

**Toxicity**

As has been our experience in the past, the toxicity accompanying fibrinolysin infusion was limited primarily to temperature elevation.[43, 44] Approximately half of the 42 infu-

**Table 10**

*Incidence of Fever Following Administration of Fibrinolysin*

| | Fever* | No fever |
|---|---|---|
| Prophylaxis | | |
| None | 7 | 6 |
| Antihistaminic | 2 | 8 |
| Barbiturate | 9 | 6 |
| Aspirin | 2 | 2 |
| | 20 (48%) | 22 (52%) |

*1 F. above baseline temperature.

**Table 11**

*Maximum Temperature Elevation Following Administration of Fibrinolysin*

| °F* | No. | Per Cent |
|---|---|---|
| 0 -1.0 | 22 | 52 |
| 1.1-2.0 | 8 | 19 |
| 2.1-3.0 | 9 | 22 |
| 3.1-4.0 | 1 | 2 |
| >4.0 | 2 | 5 |

*Above baseline value.

sions were followed by a temperature rise of more than 1 F. during the 24 hours after infusion. Various drugs were administered in an attempt to ameliorate or abort the temperature response. The regimens employed included Nembutal by the intramuscular route, 100 mg. just prior to and 6 hours after start of the infusion; aspirin, 0.6 Gm. orally just prior to and every 4 hours after infusion; and Benadryl (75 mg.) or chlortrimeton (6 to 8 mg.) intramuscularly just prior to and every 6 hours after fibrinolysin infusion was begun. The antihistaminic regimen proved the most efficacious, fever appearing in only 2 of the 10 patients treated in this manner (table 10). Observations in a series of some 200 patients treated with the same fibrinolysin preparation also have indicated that the antihistaminic schedules outlined above offer the best means of limiting the incidence and extent of fever.[31, 43, 44, 49]

The extent of the fever in this series agrees closely with that which we have reported previously, with elevations greater than 4 F. above baseline occurring in approximately 5 per cent of the cases (table 11).

The temperature elevation usually began 3 to 6 hours after the infusion was started, reached a peak at 8 to 10 hours, and subsided in the next 12 to 14 hours in almost all instances. Chills occurred in about one third of the patients who had a febrile reaction. One patient experienced a brief episode of severe epigastric pain that remains unexplained. No bleeding phenomena were noted in any patient within a 4-day period following fibrinolysin. Three patients (2 controls, 1 fibrinolysin), however, did develop bleeding while receiving anticoagulant drugs. One control and 1 fibrinolysin patient had mild hematuria. One control subject developed extensive rectal bleeding which necessitated blood transfusion.

Since fibrinolysin is derived from plasma proteins, some concern regarding possible untoward effects in patients with allergic backgrounds is warranted. In the present series, one patient with a history of bronchial asthma and another with rheumatoid arthritis received the material without significant reaction. One subject with known penicillin sensitivity developed an urticarial rash at the site of infusion. Our total experience now includes a number of patients with bronchial asthma, hay fever, and various "collagen" disorders. These patients do not have a higher incidence of febrile or other reactions than other individuals, with perhaps one exception: of 5 patients with rheumatoid arthritis who received fibrinolysin, 3 had slight to moderate increase in joint signs and symptoms some 24 to 48 hours after infusion. At the present time, therefore, the use of plasmin does not appear to be contraindicated in patients with allergic or collagen-vascular disorders, although observations in subjects with rheumatoid arthritis should be extended in this regard.

## Discussion

Theoretically, the combination of an effective thrombolytic drug with anticoagulant therapy should be more effective in the treatment of thrombophlebitis than anticoagulant

therapy alone. Acute dissolution of the offending thrombus would promptly relieve venous occlusion and hasten return of the extremity to normal. Fibrinolytic therapy also should reduce the incidence of pulmonary embolization by eliminating the embolic source, particularly since it should be most effective against the relatively fresh thrombotic zones which may be most likely to fragment. The postphlebitic syndrome, a manifestation of chronic deep venous obstruction, should be reduced in incidence and severity if thrombolysis can be achieved promptly.

The possible value of short-term thrombolytic-anticoagulant therapy in reducing the frequency of phlebitic recurrence is less clear. If recurrence is related to the speed or extent of thrombus removal following an episode of venous occlusion, the incidence of recurrence should be lowered by addition of thrombolytic agents. If, on the other hand, recurrence is determined by a primary vascular abnormality or alteration in venous blood flow, or by a hypercoagulable state that persists or returns following the phlebitic event,[53, 54] total clot removal would not alter the tendency toward recurrence. In the latter cases, only prolonged anticoagulant therapy would provide protection against redevelopment of venous thrombosis and its complications.

Several factors other than potency of the drug itself are critical in determining the clinical response to fibrinolysin.[30, 43, 44]

1. The *diagnosis* of thrombophlebitis (or other thrombotic disorders) must be established as firmly as possible. Fibrinolysin will not influence the course of cellulitis, muscle pain of traumatic or nonspecific origin, or edema due to congestive heart failure, etc. Therefore, patients were not included in this study if the diagnosis appeared equivocal or other explanations for the signs and symptoms were available.

2. An adequate *dosage* of fibrinolysin must be administered. This condition cannot be fulfilled with certainty at the present time in view of the controversy surrounding the in vivo behavior of fibrinolysin in the plasma and at the level of the clot itself.[34, 40, 45] In the present study, an acceptable dose of fibrinolysin was considered to be one that produces detectable plasma fibrinolytic activity in 90 per cent or more of patients. Previous investigations had indicated that this point was reached when 75,000 to 100,000 fibrinolytic units were administered over a 2- to 4-hour period.[31] Clinical observations also suggested that 1 such dose per 24 hours produced a clinical response in most phlebitic subjects and that repetition the second day often led to further improvement. A third dose rarely altered the course of patients who had not responded to the first 2 infusions.[43, 44] Therefore, in the present study no patient in the fibrinolysin group received more than 2 doses of fibrinolysin. Whether the regimen used in this investigation is excessive or suboptimal cannot be settled at the present time.

3. The *age of the thrombus* is probably a crucial factor in determining the success of thrombolysis. Obviously, no fibrinolytic drug can dissolve a thrombus that has become organized (i.e., in which fibrin no longer is the predominant component of the supporting framework) or which has been covered by endothelium. The time interval during which a clot remains susceptible to dissolution in a patient with thrombophlebitis is unknown. Studies on experimentally produced thrombi in the dog have indicated that success cannot be expected beyond the first 3 or 4 days.[29, 38] Obviously, these results cannot be transferred directly to man. Experimentally formed clots in the dog may be handled quite differently in terms of organization and endothelialization than a spontaneously formed human clot. Furthermore, venous occlusion in man may often be a progressive phenomenon. A venous thrombus may not be uniform in age and structure, and may contain some portions that are susceptible to lytic agents and others that are not.

Previously, definite evidence of clinical response was noted in a minority of patients when fibrinolysin was administered more than

10 days after onset of phlebitic symptoms.[43, 44] On the other hand, rapid clearing of phlebitis was almost uniformly encountered in those treated within 5 days of onset and in the majority treated between 5 and 10 days. In view of these experiences, patients with phlebitis of more than 10 days' duration were excluded from the present study. In addition, results in those patients treated within 5 days or less were analyzed separately from results in the entire group.

4. The venous clot must be *accessible* to the fibrinolytic agent. If severe arterial disease coexists in the extremity, delivery of the drug may be unsatisfactory. Also, if total occlusion exists over a long venous segment, thrombolysis is likely to be less successful than when occlusion is incomplete and involves a relatively small zone. These factors are not subject to control but should be considered in evaluating results obtained in specific patients.

5. Adequate anticoagulant therapy should be used simultaneously with fibrinolytic agents if optimum results are to be obtained. Animal investigations have indicated that rethrombosis may follow successful clot lysis unless anticoagulants are used concomitantly.[39] Our own experience has confirmed that a clinical sequence of this type may occur in patients receiving fibrinolysin alone. It should be recognized that the fibrinolytic activity of the plasma following the dosage schedule of fibrinolysin used in this study persists for a rather brief period.[31] Therefore, unless fibrinolysin is repeated or anticoagulants are administered beyond this time, the patient is not protected against the development of thrombosis. Since some thrombotic material, abnormality of the vessel wall, or clotting tendency may persist after acute clot lysis, we believe that a period of anticoagulant therapy should follow use of a fibrinolytic agent. All patients in the fibrinolysin series received such combined therapy.

Having explored the problems surrounding study in this area, we may now turn to evaluation of the results obtained in this particular investigation. Considering first the total series, we find data that strongly suggest that the combined fibrinolysin-anticoagulant regimen is superior to the anticoagulant drugs alone in attaining the "short-term" goals of therapy. Loss of pain and edema as well as the return of leg size to normal all occurred more promptly in those receiving combined therapy. This hastened resolution of phlebitic signs and symptoms carried with it the benefits of earlier ambulation, a shorter period of anticoagulant therapy, and a shorter hospital stay. The superiority of combined therapy is maintained whether actual values or the adjusted "arbitrary" values are considered. Therefore, one of the benefits we hoped to derive from combined therapy was achieved, viz., earlier return of the patient to functional status.

The second objective, prevention of pulmonary embolization, seems to have been achieved although conclusions in this regard must be drawn with caution. Three nonfatal and 1 "possible" fatal pulmonary embolus in the controls during the 2-week period after start of anticoagulant therapy contrast with the single "possible" nonfatal embolus in the fibrinolysin group. Such a low incidence in the latter patients is especially noteworthy when it is recalled that some 28 per cent of this group had suffered an embolus preceding institution of therapy and such patients are especially prone to develop further embolic episodes.[17] The low incidence of embolization in the group receiving combined therapy also indicates that the release of embolic material by fibrinolytic agents seem unlikely.

Attainment of the third objective, prevention of postphlebitic residual, was less clearly influenced by fibrinolysin. The incidence of this complication was quite low in both groups, however, especially in view of the high incidence of femoral and iliofemoral occlusion which characterized the entire series.[35] Definite conclusions regarding the ability of fibrinolysin to reduce the incidence or extent of postphlebitic residuals must be deferred.

The data regarding early recurrence are also rather difficult to interpret. While all

patients receiving combined therapy did escape early recurrence versus 2 recurrences in the controls, the small numbers involved preclude any firm statements on this point.

The "long-term" results of this series are of special interest. It is apparent that even prompt therapy with either fibrinolysin plus the anticoagulant drugs or with the latter alone does not prevent late recurrence of phlebitis or embolism. Indeed, the incidence of late recurrence is rather high in both groups. Pulmonary embolization did occur less frequently in the fibrinolysin group and, while it is tempting to attribute this to therapy, more complete follow-up data in larger series are needed to warrant this conclusion. The redevelopment of thrombosis or embolism can be interpreted in various ways. One may presume that therapy has been ineffective to the extent that thrombotic material remains after the acute episode and serves as a nidus for recurrent formation of clot. On the other hand, local vascular abnormalities may exist which produce moderate degrees of stasis and, alone or in the presence of a temporary thrombotic state, precipitate the original thrombosis and can lead to its renewal. This latter possibility is supported by the investigations of Wessler.[53, 54]

In terms of over-all mortality, the long-term results also are revealing. The 17 per cent mortality in the controls is a rather imposing figure in view of the limited period of follow-up, especially since embolization was at least a contributory factor in the death of 4 patients and probably the immediate cause of death in the fifth. In the fibrinolysin group, only 2 deaths are known to have occurred—one due to carcinoma of the pancreas and the other due to uremia. While the inference may be drawn that fibrinolysin therapy has reduced mortality due to early and late embolization, again more extensive data must be obtained before such conclusions are justified.

The analysis of the "early treatment" subgroups was carried out to test the hypothesis that the age of the thrombus will influence response of the phlebitic subject to fibrinolysin. If this were so, differences between the fibrinolysin and control subgroups should be greater than those that exist between the two total groups. This expectation appears to be confirmed in regard to "short-term" results, especially in terms of response of the extremity itself. When analysis is limited to those treated promptly, the differences in phlebitic course (table 7) between the control and treated groups become wider and more significant statistically. The absence of either early (within 2 weeks) embolization or recurrence in the fibrinolysin subgroup is also noteworthy, although the incidence of postphlebitic residuals is not appreciably lower than in the controls.

As in the "total groups," however, the apparent superiority of combined therapy is not so evident when long-term results are considered. While embolic incidence and mortality are lower in the fibrinolysin group, these data may be influenced by the follow-up period available in each group. Furthermore, the tendency toward recurrence does not appear to have been diminished in those receiving fibrinolysin.

Finally, in assessing the over-all value of fibrinolysin, we cannot neglect consideration of its toxicity. The present study has confirmed our previous impressions that the febrile response to this agent, while undesirable, does not impair its application in the great majority of patients with acute thrombophlebitis. However, antihistaminic prophylaxis is especially important in patients with underlying disorders that might be unfavorably influenced by a short period of fever or chills (e.g., coronary artery disease). The possible risk of reaction in such individuals must be weighed against the expected benefits. Other theoretic dangers of fibrinolysin therapy, such as embolization or hemorrhage, have not proved of clinical importance. It should be recognized, however, that these statements regarding toxicity of the material apply only to the dosage regimen employed in these patients.

In addition to the information regarding

the effect of fibrinolysin, the present study also supplies some data in an area that is relatively unexplored; namely, the long-term prognosis of phlebitic subjects. The majority of patients with thrombophlebitis recover completely after a relatively short period of bed rest and anticoagulant therapy. In the present series, the morbidity and mortality in both groups would have been extremely low if we had discontinued our observations after a 2-week period or at the time of hospital discharge. Indeed, the results would compare with the most favorable reported in other series regarding incidence of embolization and other complications. When data obtained during follow-up are analyzed, however, the picture is altered. It seems evident that whether combined therapy or anticoagulant therapy alone is used—regardless of the apparent restoration of the phlebitic extremity to a clinically normal state—patients recovered from deep thrombophlebitis have a significant long-term risk of recurrent venous occlusion and pulmonary embolism. Whether this should alter our concepts of management in terms of prolongation of anticoagulant therapy or repetition of fibrinolysin beyond the acute episode requires consideration. Certainly, if further study confirms the data offered here, such a revision may be indicated, since such measures are generally considered unnecessary at the present time. While addition of fibrinolysin to the initial regimen may improve the long-term outlook, acceptance of this as fact must also await further investigation.

Finally, we must emphasize that the fibrinolytic-anticoagulant regimen used in the present study may be less than ideal. Even after many years of widespread use, no criteria for "ideal" anticoagulant therapy with heparin or the coumarin-type drugs have been universally accepted.[23] Therefore, it would seem unlikely that the "ideal" dosage schedule of fibrinolysin, or any fibrinolytic agent, will be generally agreed upon in the near future, especially in view of continued uncertainty regarding the behavior of fibrinolytic agents in vivo.

For the present we must continue to select fibrinolysin dosage on a rather empiric basis supported by experimental data derived from available laboratory methods. As clinical experience expands and laboratory methods improve, it may become apparent that multiple or continuous infusions at higher dosage levels are more effective than those used in the present study. Clinical studies at higher dosage levels are feasible, since we have demonstrated the safety of fibrinolysin in doses well above 100,000 units per 3 hours.[49] Only further investigation will establish whether larger doses than those used here will prove more effective in the treatment of acute deep venous occlusion.

In our opinion, the present study indicates that at least the first few steps have been taken toward the ultimate goal of establishing a method for safely and effectively dissolving intravascular clot in man. It is quite likely that continued research will ultimately lead to development of more ideal thrombolytic agents in terms of ease and administration, absence of toxicity, of precise determination of dosage required to achieve the desired effects.

## Summary

Sixty-two patients with deep thrombophlebitis of less than 10 days' duration were studied in controlled fashion. Thirty "control" patients were treated by routine methods including anticoagulant drugs. Thirty-two "treatment" patients received fibrinolysin (plasmin) in addition to control therapy.

The composition of the groups studied and the protocol followed are presented in detail.

Comparison of the 2 groups indicates that the addition of fibrinolysin to the therapeutic regimen leads to more rapid clearing of the acute phlebitic episode and may diminish the short-term incidence of phlebitic recurrence and pulmonary embolization. Postphlebitic residuals were encountered with almost equal frequency in both groups.

Greater short-term differences in therapeutic response exist between control and fibrinolysin patients when analysis is restricted to

those treated within 5 days of phlebitic onset.

The available data do not permit firm conclusions regarding the apparently favorable influence of fibrinolysin upon the long-term prognosis of phlebitic subjects, but do indicate that recurrence and embolization can be expected in both groups.

The factors that may influence the results obtained with fibrinolytic therapy are discussed and the importance of considering them in studies of this type is emphasized.

### Acknowledgment

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### Summario in Interlingua

Sexanta-duo patientes con thrombophlebitis profunde de minus que 10 dies de duration esseva studiate sub conditiones a controlo. Trenta patientes, representante le gruppo de controlo, esseva tractate secundo le methodos routinari, incluse le uso de drogas anticoagulante. Trenta-duo patientes, representante le gruppo de tractamento, recipeva fibrinolysina (plasmina) a parte le therapia de controlo.

Le composition del gruppos studiate e le technica experimental usate es presentate in detalio.

Le comparation del 2 gruppos indica que le addition de fibrinolysina al regime therapeutic resulta in un plus rapide resolution del episodio phlebitic acute e reduce possibilemente le incidentia a curte vista de recurrentias phlebitic e de embolisation pulmonar. Residuos postphlebitic esseva incontrate in le duo gruppos con quasi le mesme frequentia.

Plus notabile differentias immediate in le responsa therapeutic existe inter le patientes tractate con fibrinolysina e le patientes de controlo si le analyse es restringite a casos tractate intra 5 dies post le declaration del phlebitis.

Le datos currentemente disponibile non permitte firme conclusiones con respecto al apparentemente favorabile influentia de fibrinolysina super le prognose a longe vista pro le subjectos phlebitic, sed ille datos indica que recurrentias e embolisationes pote esser expectate in ambe gruppos.

Le factores que affice possibilemente le resultatos obtenite per le therapia fibrinolytic es discutite. Le importantia de prender los in consideration in studios de iste typo es sublineate.

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## Vesalius

During Vesalius' absence from Padua, after the appearance of his book, the storm broke out. The great Sylvius and others thundered against him, reviling him in a free flow of adjectives. Coming back to Padua, after about a year's absence, he found opposition to his new views strong even there, not the least active among his opponents being his old pupil Columbus. He gave lectures at Padua, offering to test publicly in the dissecting theatre whether his statements were wrong or no. He lectured also at Bologna, and at Pisa, where the enlightened Cosimo de' Medici of Florence would willingly have detained him as professor in the University which he was nursing. But such tokens of encouragement and others like them weighed before him little when compared with the bigoted opposition of so many of his brethren. The spirit shewn by the latter entered like iron into his soul. If the work on which he had laboured so long and which he felt to be so full of promise met with such a reception, why should he continue to labour? Why should he go on casting his pearls before swine? He had by him manuscripts of various kinds, the embodiment of observations and thoughts not included in the *Fabrica*. What they were we can only guess; what the world lost in their loss we shall never know. In a fit of passion he burnt them all, and the Emperor Charles V., offering him the post of Court Physician, he shook from his feet in 1544 the dust of the city in whose University he had done so much, and still a youth who had not yet attained the thirties ended a career of science so gloriously begun.—Sir M. Foster. *Lectures on the History of Physiology*. London, Cambridge University Press, 1901.

# The Prophylactic Value of Long-Term Anticoagulant Therapy

*By* A. Boyd Thomes, M.D., Raymond W. Scallen, M.D., and I. Richard Savage, Ph.D.

SINCE the discovery of Dicumarol by Link in 1939, many papers have appeared on the use of anticoagulants in various thromboembolic conditions. Marple and Wright[1] have provided an extensive review of the literature up to 1950 covering theoretical aspects of the problem and results of treatment in many, chiefly acute, conditions.

Beginning in 1944 with the initial report of Nichol and Fawcett,[2] long-term, or prophylactic, anticoagulant therapy has received increasing attention in different thromboembolic conditions. In 1957, Bjerkelund[3] reviewed the many published reports on long-term therapy in myocardial infarction. The few papers on treatment in cerebral vascular disease were reviewed in the report of the *Second Conference on Cerebral Vascular Diseases*, edited by Wright and Millikan.[4]

Despite the developing abundance of reports the prophylactic value of long-term anticoagulant therapy remains equivocal, largely because many of the studies lack suitable controls and do not lend themselves to statistical analysis. Although most of the reports have found the treatment beneficial, they do not make clear the degree to which this is the case; nor are indications for treatment or discontinuance entirely agreed upon. Furthermore, there are not yet adequate data with which to estimate the probability of recurrence and death during and after discontinuing treatment. The present report attempts to clarify these questions.

### Rationale of Anticoagulant Therapy

Whether or not a hypercoagulable state exists in thromboembolic conditions, a local surface or disease process must be present, since clotting does not occur throughout the entire vascular system but only in local areas. The experimental and clinical evidence suggests that under normal circumstances the intima maintains a negative charge from a continuous layer of negatively charged heparin-like material. With intimal damage there presumably is a reversal or reduction of the negative charge; this alteration is associated with the disappearance of heparin-like properties and with the appearance of cephalin-like material at the surface, giving rise to platelet stickiness. As a result, thrombosis may occur when the blood components are in a condition to respond to these intimal changes. If such a hypothesis is correct, heparin would be valuable in affecting the intimal cells and in neutralizing any circulating, active plasma thromboplastin (factor V or ac-globulin). Heparin might also prevent platelet stickiness and, in large doses, might exert an antithrombic effect. Antiprothrombin drugs also may decrease activity of plasma thromboplastin component; they are known to decrease the activity of plasma thromboplastin antecedent (factor VII), which is necessary for the normal action of tissue thromboplastin.[5]

In coronary and cerebral arterial diseases atherosclerosis is generally recognized as the primary process. Considerable disagreement, however, exists as to the pathogenesis of atherosclerosis. Until recently the general opinion has been that atherosclerosis begins as a degenerative change with a deposition of cholesterol in the deep layers of the intima followed by fibrous tissue proliferation. Recently Duguid and Robertson[6] have revived interest in the old theory of Rokitansky,[7] who stated that atheroma was the result of excessive deposition of blood derivatives, parti-

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lly fibrin, on the inner surface of the arteries. Some experimental evidence has subsequently supported this view, i.e., that fibrinous thickening of the intima with narrowing of the lumen can result from gradual organization of thrombi in the arteries. Thus thrombogenic intimal changes may ultimately form a site for secondary thrombotic deposition. Continuous and prolonged anticoagulant therapy may therefore be of significance in preventing further development of atherosclerosis as well as in preventing thrombosis at the site of an atherosclerotic plaque.[8-11] Experimental evidence also indicates that anticoagulant therapy increases the natural tendency to recanalization of occluding thrombi.[12]

A wide variety of circumstances have been suggested as causes of the hypothetical state of hypercoagulability. These include a postprandial hypercoagulability that is apparently related to the intake of saturated fatty acids. It is believed that such a condition would be minimized by prolonged anticoagulant therapy.[5]

Thrombolysis must also be considered in the pathogenesis of thrombosis. Grieg and Rundle[13] have demonstrated in vitro a marked reduction in fibrinolysis in the plasma of subjects after a high-fat meal; they have found, however, that the lipemia resulting from the ingestion of *unsaturated* fatty acids does not inhibit fibrinolysis. If postprandial inhibition of fibrinolysis does occur, then the other factors involved in thrombogenesis should be minimized by the use of anticoagulants.

## Methods and Material

The present study is an evaluation of the results of long-term anticoagulant therapy in a group of 336 patients encountered in a stable urban midwestern practice with various thromboembolic conditions, classified as follows: 1. Coronary disease: myocardial infarction, mild, moderate, or severe; impending infarction; angina pectoris. 2. Cerebral vascular disease: involving carotid or vertebral-basilar arterial system, transient, progressive, or complete. 3. Phlebitis: classified as to site. 4. Pulmonary embolism: single or multiple. 5. Peripheral arterial thrombosis or embolism: classified as to site.

To achieve uniformity the diagnoses were all reevaluated at the time of classification.

Anticoagulant therapy (90 per cent of patients received Dicumarol, Danilone, or Cumopyran) was usually started in the hospital, although in some instances it was initiated in ambulatory patients. Prothrombin times as a rule were measured daily during hospitalization and less frequently on long-term programs with outpatients. With most long-term patients, prothrombin time determinations were made every 3 weeks with the Quick 1-stage method. A "therapeutic prothrombin time" has been arbitrarily defined as falling between 18 and 35 seconds. The control was almost always 12 seconds or less.

The study is entirely a retrospective evaluation and is in no sense a planned experiment. Accordingly, various therapeutic measures in addition to anticoagulant treatment were used.

The present report compares the rates of first nonfatal recurrence in persons on continuous anticoagulant therapy with the rates after discontinuing therapy in the entire group. It further presents the mortality rates, and describes the pattern of recurrence after discontinuance of therapy in persons with brief, intermediate, and prolonged initial periods of continuous therapy.

To manage the large and varied assortment of data a code sheet of 80 items was filled out for each patient; the data on this sheet were then transferred to IBM punch cards for sorting analysis. The items recorded include the initial diagnosis; various biographical data (sex, age, occupation, ethnic group, height and weight, family history, past history of prior thromboembolic and other significant diseases); laboratory data; electrocardiographic measurements; appropriate time measurements; the nature and dates of first and subsequent recurrences during therapy and after therapy; the incidence and nature of hemorrhagic complications; the stability of office and hospital prothrombin times; subsequent clinical status of the patient; and the incidence, time, and nature of death.

All thromboembolic episodes occurring after the episode leading to inclusion in the study were considered to be recurrences. Episodes of prolonged angina were classed as recurrences, even though the diagnosis of infarction could not always be made. Likewise, transient attacks of cerebral arterial insufficiency were included, despite the fact that some of these may not have been thromboembolic in origin.

Three time-periods were used in the evaluation. The first, called the "total period of observation," was measured from the date on which the patient was first seen for the episode leading to inclusion in the study until the date on which the patient's

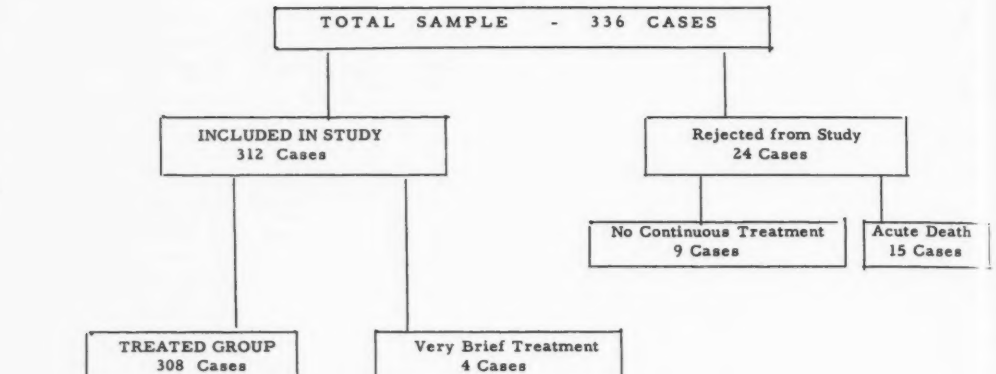


**Figure 1**

*Analysis of 336 cases.*

chart was drawn for coding or the date of death. This period was then subdivided into an initial period called the "duration of continuous therapy" and a subsequent period called the "period of observation after first discontinuance."

The "first nonfatal recurrence on continuous therapy" was measured on the time-scale dating from the date of inclusion in the study and corresponding to the scale used for "duration of continuous therapy." The "first nonfatal recurrence after discontinuing therapy" was measured from the date of the first discontinuance of therapy and corresponds to the time-scale covering the "period of observation after the first discontinuance." The death time-scales are similar.

For easy interpretation, comparison, and determination of the statistical significance and reliability of the results, the method of constructing survivorship tables[14] has been chosen. This method consists in determining rates of death or first recurrence at successive periods of time. Then the estimated number of persons per original 1,000 with nonrecurrence or survival at successive time periods can be determined. The standard errors of these estimates of the number of survivors were used to compute the significance of differences noted in various groups.[15] (See Appendix.)

### Comparison of the Groups

The general outline of anticoagulant therapy for the entire sample of 336 cases is shown in figure 1. Patients who died in the first month (acute death) were excluded from the study, as were those who received only heparin (no continuous treatment). For simplicity's sake, the term "treated group" is used to describe the 308 patients who had a period of continuous treatment; the term "discontinued group" to describe the 203 observed after discontinuing treatment (including 4 patients whose treatment was very brief); and the term "never-discontinued group" to describe the 109 patients who received treatment throughout their entire period of observation. Substantially, then, the "treated group" consists of the "discontinued group" plus the "never-discontinued group."

Tables 1 to 4 compare the diagnostic composition, age and sex, prior thromboembolic history, and associated pathologic conditions in the discontinued and the never-discontinued groups. As compared with the discontinued group, the never-discontinued group is seen to contain a larger percentage of cases of coronary and cerebral arteriosclerosis, patients of somewhat greater average age a higher incidence of prior thromboembolic

episodes and of angina pectoris, and a larger percentage of prior abnormal electrocardiograms. The incidence of hypertension, cardiac decompensation, and diabetes is similar in the 2 groups.

Thus, the 109 patients in the never-discontinued group are clearly shown to be poorer risks by virtue of age, sex, prior history, and associated pathologic conditions. Moreover, the greater severity of involvement in those who were continued on treatment was noted uniformly for each disease category.[16, 17]

The patients in the discontinued group did in fact show a lesser tendency to have thromboembolic recurrences during their period of continuous therapy. Compared with the patients whose therapy was never discontinued, they had a lower incidence of recurrence during the first year on therapy and no recurrences during the subsequent course of treatment.

### The Use of the Discontinued Group as a "Control"

Comparison of the rates of first nonfatal recurrence during therapy and after discontinuing therapy raises the question of the validity of using the discontinued group as a "control" to be compared with the treated group. In the present study the use of the discontinued group as a control can be justified in several ways:

1. The discontinued group originally comprised two thirds of the treated group, and it thus serves as a control for itself (tables 1 to 4).

2. The never-discontinued group (the remaining third of the treated group) has been shown to be actually a poorer risk group than the discontinued group.

3. The incidence of recurrence among the members of the discontinued group while on the initial continuous treatment was not higher than that for those who remained on treatment.

4. Unfavorable response to treatment and complications of treatment were not significant factors in determining discontinuance. The reasons for discontinuing treatment were indication over (121 instances), initiative of patient (35 instances), other diseases or operation (30 instances), and complication of treatment (13 instances). Of the 13 who discontinued because of complications, 4 died and 2 had nonfatal recurrences in the first year after discontinuance. These numbers are not large enough to affect the first-year recurrence and death rates substantially.

**Table 1**

*Comparison of Discontinued and Never-Discontinued Groups: Diagnostic Categories*

| | Observed after discontinuing therapy | | Never discontinued | |
|---|---|---|---|---|
| | No. patients | % | No. patients | % |
| Coronary | 84 | 41 | 75 | 69 |
| Cerebral vascular accident | 40 | 20 | 19 | 17 |
| Phlebitis | 49 | 24 | 5 | 5 |
| Pulmonary embolism | 15 | 7 | 5 | 5 |
| Peripheral thrombosis | 15 | 7 | 5 | 5 |
| Total | 203 | | 109 | |

## Results

### Incidence of First Nonfatal Recurrence

None of the patients in the discontinued group received anticoagulant therapy after its discontinuation, in the absence of recurrence. Thus in the time periods being considered the entire treated group was on therapy, and the entire discontinued group was off therapy.

During the first year of continuous therapy, there were 23 nonfatal recurrences; of these 16 occurred with subtherapeutic prothrombin times and 7 with therapeutic prothrombin times. In the second year there were 2 recurrences with subtherapeutic prothrombin times, and, thereafter, none occurred with subtherapeutic prothrombin times.

The pattern of first nonfatal recurrence during therapy and after discontinuing therapy is shown in table 5. The first year on treatment is subdivided into 4 smaller units to record changes in rate during that period. The rates are based on the ratio of the num-

**Table 2**

*Comparison of Discontinued and Never-Discontinued Groups: Age and Sex*

| | | Observed after discontinuing therapy | | | | Never discontinued | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. patients | | % | | No. patients | | % | |
| Sex | Male | 114 | | 56 | | 85 | | 78 | |
| | Female | 89 | | 44 | | 24 | | 22 | |
| | | Male | | Female | | Male | | Female | |
| | | No. pts. | % | No. pts. | % | No. pts. | % | No. pts. | % |
| Age | 20—29 | 2 | 2 | 3 | 3 | | | | |
| | 30—39 | 7 | 6 | 6 | 7 | 4 | 5 | 1 | 4 |
| | 40—49 | 18 | 16 | 16 | 18 | 12 | 14 | 2 | 8 |
| | 50—59 | 33 | 29 | 19 | 21 | 30 | 35 | 7 | 9 |
| | 60—69 | 35 | 31 | 26 | 29 | 27 | 32 | 6 | 5 |
| | 70—79 | 17 | 15 | 18 | 20 | 10 | 12 | 6 | 5 |
| | 80—89 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 8 |
| | Average age | 58 | | 58 | | 58 | | 63 | |

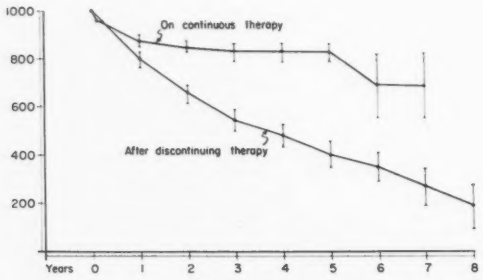


**Figure 2**

*Time of first nonfatal recurrence* (abscissa). *Number of persons with no recurrence of original hypothetical groups of 1,000* (ordinate). *Brackets enclose ± 1 standard error of the estimate of the number of persons with no recurrence.*

ber with no recurrence during the time period to the number exposed to the risk of having a first nonfatal recurrence. It is important to note that a patient who has had a first nonfatal recurrence may remain on therapy, but no longer be exposed to the risk of having a *first* nonfatal recurrence, having already had one. Such a patient would of course continue to be exposed while on therapy to the risk of death.

The table indicates the number of persons in every 1,000 who would have had no recurrence during successive time periods. The numbers in parentheses indicate the standard errors of these estimates.

This table allows quick comparison of the fate of persons who remained on continuous treatment with the fate of those who discontinued. The lower section of table 5 presents the rate of first nonfatal recurrence after discontinuing therapy. The first year after discontinuing therapy is not subdivided. Approximately 821 persons would have had no recurrence after 60 months on continuous therapy as compared with 396 with no recurrence 60 months after having discontinued therapy.

Figure 2 presents the data from table 5 in graphic form. The curves show the number of persons who could be expected to have no recurrence at the successive intervals indicated on the time scale. The brackets enclose ±1 standard error. The rate of recurrence in the group on treatment is initially high and rapidly diminishes during the first few months, the curve becoming nearly horizontal by the end of the first year. The rate remains low throughout the first 5 years. The drop at the end of the curve is associated with a very small number of cases, and the standard error of the estimate is therefore greater. The curve for the recurrence rate in persons who discontinued therapy is also high initially, but, by contrast, it remains high throughout the period of observation.

**Effects of Different Durations of Continuous Treatment on the Recurrence Rates after Discontinuing Therapy**

The patients in whom treatment was discontinued were separated into those whose

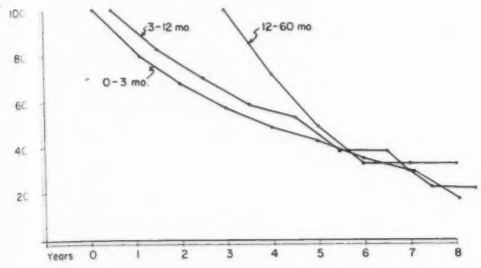


**Figure 3**

*Number of persons with no recurrence of original hypothetical groups of 1,000* (ordinate) *for number of years* (abscissa) *after discontinuing therapy in groups with different durations of initial treatment.*

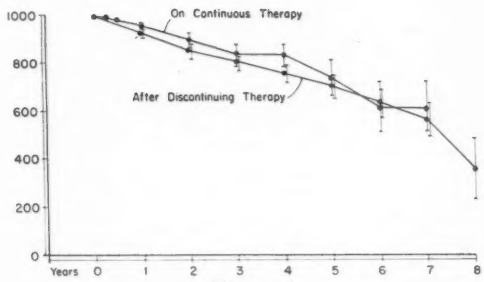


**Figure 4**

*Number of survivors of original hypothetical group of 1,000* (ordinate) *for number of years* (abscissa) *on continuous therapy and after discontinuance of therapy. Brackets enclose ± 1 standard error of the estimate of the number of persons surviving.*

initial treatment was brief (0 to 3 months), intermediate (3 to 12 months), and long (12 to 60 months).* The rate of first nonfatal recurrence after discontinuing therapy was determined for each of the 3 groups (fig. 3). The date of onset of the prior continuous therapy was used as the zero time point, and the rate curves begin at the average time of discontinuance for the 3 groups. The 3 curves merge at 40 per cent still free of recurrence in 5½ years. The recurrence rate for patients who were treated longer initially is somewhat greater after discontinuance.

### Death Rates during Treatment and after Discontinuation

In comparison of the mortality in the treated and discontinued groups it must be noted that the discontinued group includes a substantial number of patients whose therapy had been resumed after a nonfatal recurrence. As far as mortality is concerned, then, the discontinued group is to be viewed as a group on intermittent therapy.

Eighteen deaths occurred in the group on continuous treatment. Of these, 1 occurred with a subtherapeutic prothrombin time, 2 occurred with a prothrombin time greater than 40 seconds (the prothrombin time determination nearest to the time of the fatal episode), and 15 occurred with a prothrombin time in the therapeutic range. There were 46 deaths in the discontinued group.

The mortality rates are shown in figure 4. Since the range of ±1 standard error overlaps at each anniversary (brackets), no significant difference exists between the 2 curves. The group on continuous treatment has a somewhat lower death rate for the first 5 years, after which the rates are about the same. At the end of 5 years, approximately 737 persons of an original 1,000 would have survived in the group on continuous therapy. In the group observed after discontinuing therapy, 702 of 1,000 would have survived. The larger percentage of more serious cases in the group treated for prolonged periods probably affects its later mortality adversely.

### Effects and Complications of Treatment

When treatment was initiated during hospitalization, a prothrombin time of 20 seconds or more was achieved by the third morning of hospitalization in 92 per cent of the cases. During hospitalization the prothrombin time was in the therapeutic range 80 per cent or more of the time in 80 per cent of the cases. The percentage of prothrombin times in the therapeutic range was computed for each patient who had had office prothrombin determinations. The average of these per-

* The curve for the group with brief initial treatment is based on 118 cases exposed to the risk of having a first nonfatal recurrence after discontinuing therapy. The intermediate group curve is based on 40 cases, and the more prolonged group curve is based on 24.5 cases.

**Table 3**

*Comparison of Discontinued and Never-Discontinued Groups: Prior Thromboembolic Conditions*

| | Observed after discontinuing therapy | | Never discontinued | |
|---|---|---|---|---|
| | No. patients* | % | No. patients* | % |
| Prior myocardial infarct | 21 | 10.5 | 24 | 22 |
| Prior angina pectoris | 40 | 20 | 31 | 28 |
| Prior cerebral vascular accident | 14 | 6.5 | 12 | 11 |
| Prior phlebitis or pulmonary embolism | 19 | 9 | 8 | 8 |
| Prior retinal thrombosis | 3 | 1 | 1 | 1 |
| No prior episode | 126 | 62 | 53 | 49 |

*Multiple classification possible.

centages was 70.4 per cent. Little difference in the average stability of prothrombin control was observed with longer or briefer periods of treatment.

Hemorrhagic complications were observed in 19 per cent of the patients, with 12 per cent having only 1 episode, 5 per cent having 2 episodes, and 3 per cent having 3 or more episodes. Of a total of 95 bleeding episodes, 78 were considered minor, and 17 were considered severe. Two deaths occurred in patients whose prothrombin times were greater than 40 seconds.

## Discussion

The pattern of first nonfatal recurrence in persons on continuous therapy was described in table 5. This table can be thought of also as presenting the probability of remaining free from subsequent recurrence. Two important factors must be considered in viewing the first recurrence rates on continuous therapy: (1) the tendency to recurrence is very strong during the immediate post-thrombotic period; and (2) anticoagulant therapy requires some time to become established. During the first month the recurrence rate is 3.6 per cent. Thereafter, the rate decreases to an average of 1.25 per cent, 0.73 per cent, and 0.85 per cent per month for the remaining 3 time periods of the first year. The average monthly rate during the second year is only 0.26 per cent. Thus, once the initially high rates have passed,

**Table 4**

*Comparison of Discontinued and Never-Discontinued Groups: Associated Pathologic Conditions*

| | Observed after discontinuing therapy | | Never discontinued | |
|---|---|---|---|---|
| | No. patients* | % | No. patients* | % |
| Hypertension | 74 | 36 | 36 | 3 |
| Elevated serum cholesterol | 6 | 3 | 12 | 1 |
| Enlarged heart | 15 | 7 | 10 | |
| Cardiac decompensation | 19 | 9 | 9 | |
| Uremia or renal insufficiency | 3 | 1 | 4 | |
| Diabetes | 15 | 7 | 5 | |
| Valvular disease | 6 | 3 | 5 | |
| Postoperative or posttraumatic | 36 | 17 | 6 | 6 |
| Atrial fibrillation | 11 | 5 | 6 | 6 |
| Prior abnormal electrocardiogram | 54 | 27 | 38 | 35 |
| Varicose veins | 13 | 6 | 7 | 6 |

*Multiple classification possible.

the likelihood of further nonfatal recurrence remains small.

During the first year on treatment a subtherapeutic prothrombin time was frequently associated with recurrence. Despite the relative frequency of subtherapeutic prothrombin times in later years, associated recurrence almost never took place.

Thus, the rate of recurrence in patients on continuous therapy appears to be initially high. The early high rate suggests the importance of maintaining therapeutic prothrombin time levels during the first several months. Coincident with the establishment of anticoagulant therapy, the recurrence rate becomes lower rapidly and approaches zero for several years. At the end of 5 years, 821 of the original hypothetical 1,000 receiving treatment continuously would have had no recurrence (table 5).

The pattern of recurrence in patients who discontinued therapy is quite different. In this group the recurrence rate is high during the first year after discontinuing therapy, namely, 20.9 per cent or about 1.74 per cent per month. This average rate per month is not so high as the rate observed for the first month on con-

tinuous therapy; but in the discontinued group the rate of recurrence *remains* high, with no sign of the tendency to level out observed in the group on continuous therapy. That is, at the end of 5 years, only 396 persons of 1,000 who had discontinued treatment would still be free of recurrence. The difference in rate of first nonfatal recurrence has been shown to be statistically significant throughout the period of observation. (See Appendix.)

To date there has been no useful guide to the indications for discontinuing anticoagulant therapy. The decision to discontinue should be made when the patient is presumably as safe off therapy as he is on therapy. The curves in figure 2 show clearly that the tendency to recurrence after discontinuance is not favorably affected by a longer duration of initial continuous therapy. There appears to be no significant difference between the rates of recurrence after discontinuance following brief (0 to 3 months) and intermediate (3 to 12 months) durations of initial therapy. Following more prolonged initial therapy (average of 3 years) the rate of recurrence after discontinuance actually appears to be higher. It is true that the latter group contains a higher percentage of coronary cases and a smaller percentage of venous thromboembolic cases.

These data indicate that maintaining anticoagulant therapy does not arrest the underlying disease process and that upon discontinuance, the thrombotic tendency again becomes manifest and even shows a tendency to "catch up." Thus, the evidence suggests that there is no time when it is safe to discontinue anticoagulant therapy in the more serious thromboembolic diseases.

## Appendix

The estimates of numbers of survivors or nonrecurrors per 1,000 (table 5), involve statistical variations. The standard errors of these estimates can be used in the following ways: 1. The interval equal to the "number of survivors plus or minus twice the standard error" will cover the "true" or "long-run average" of the number of survivors 95 per cent of the time. 2. The standard errors can be used to determine the significance of differences between 2 groups. To test the hypothesis that the treated group has a larger number of nonrecurrors than the discontinued group, the observed difference in the number with no recurrence is compared with the square root of the sum of the squared estimates of the standard errors. If the observed difference is greater than 1.65 times the latter figure, the difference can be considered significant at the 5 per cent level. Thus, to compare the treated group with the discontinued group at 1 year, for example, the difference in the observed number of cases with no recurrence is 81 (table 5), while 1.65 times the square root of the sum of the squares of the estimates of the standard errors is only 66; therefore the difference is significant. Since a band of 1 standard error has been marked off in the graphs around each estimate of the number of persons with no recurrence, and these standard errors for the 2 groups are similar at corresponding time intervals, the differences can be considered significant if the

**Table 5**

*First Nonfatal Recurrence on Continuous Therapy*

| Time interval[1] | Observed percentage with no recurrence | Number with no recurrence ÷ number exposed to risk | Estimated no. with no recurrence for 1000 patients |
|---|---|---|---|
| 0 | 96.4 | 266.0/276.0 | 1000 |
| 1 month | 97.5 | 192.5/197.5 | 964 (11)* |
| 3 months | 97.8 | 132.5/135.5 | 940 (15) |
| 6 months | 94.9 | 92.5/97.5 | 919 (19) |
| 12 months | 96.9 | 62.5/64.5 | 872 (27) |
| 24 months | 97.2 | 34.5/35.5 | 845 (33) |
| 36 months | 100 | 17.5/17.5 | 821 (39) |
| 48 months | 100 | 10.5/10.5 | 821 (39) |
| 60 months | 83.3 | 5.0/6.0 | 821 (39) |
| 72 months | 100 | 2.0/2.0 | 684 (129) |

*First Nonfatal Recurrence after Discontinuing Therapy*

| Time interval[2] | Observed percentage with no recurrence | Number with no recurrence ÷ number exposed to risk | Estimated no. with no recurrence for 1000 patients |
|---|---|---|---|
| 0 | 79.1 | 148.0/187.0 | 1000 |
| 12 months | 82.4 | 98.5/119.5 | 791 (30) |
| 24 months | 82.8 | 62.5/75.5 | 652 (37) |
| 36 months | 88 | 36.5/41.5 | 540 (42) |
| 48 months | 83.3 | 20.0/24.0 | 475 (46) |
| 60 months | 87.5 | 14.0/16.0 | 396 (53) |
| 72 months | 78.9 | 7.5/9.5 | 346 (57) |
| 84 months | 66.7 | 2.0/3.0 | 273 (64) |

*The numbers in parentheses indicate the standard error of the estimate of the number of persons with no recurrence.

[1]Time measured from date of inclusion in study.

[2]Time measured from date of discontinuance.

bands are separated by 0.3 or more of 1 standard error.

Thus, the treated group has a significantly greater number with no recurrence at the end of the first year and throughout the period of observation (fig. 2).

In interpreting the statistical analysis 2 technical points should be made. Insofar as the discontinued group represents a (random) sample of the treated group, the estimates of rates and differences of rates in the various groups are unbiased; i.e., the averages of these rates for large samples would correspond to the population values. The standard deviations for a single group are valid whenever the estimate of the rate is unbiased. In comparing 2 groups with the use of the standard deviations, the results are correct with no further assumptions when the groups are disjoint, e.g., never-discontinued and discontinued. To use the standard deviations when the groups are not disjoint, e.g., continuous therapy and discontinued therapy, one would need to assume exponential survival distributions.[18]

### Acknowledgment

The authors wish to thank Professor Henry W. Riecken, Department of Sociology, University of Minnesota, for his generous assistance with the preparation of the code sheet and Mr. James S. Barden, Assistant Director Research Division, School of Journalism, University of Minnesota, for operating the IBM counting-sorter.

### Summario in Interlingua

In recente tempores, therapia anticoagulante a longe vista pro le prevention de morbo thromboembolic ha essite un thema de considerabile interesse. In le presente studio un meticulose tentativa esseva facite de evalutar su efficacia in un grande gruppo de patientes incontrate in practica private.

Le resultatos del studio indica que mantener therapia anticoagulante non arresta le subjacente processo pathologic e que, post les discontinuation del therapia, le tendentia thrombotic redeveni manifeste e mesmo revela un certe intensification. Isto significa que il non existe un momento al qual il es salve discontinuar le therapia anticoagulante in casos del plus serie morbos thromboembolic.

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# Differentiation of Interatrial Communications by Clinical Methods

## Ostium Secundum, Ostium Primum, Common Atrium, and Total Anomalous Pulmonary Venous Connection

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THE 4 forms of interatrial communication —ostium secundum, ostium primum, common atrium, and total anomalous pulmonary venous connection—are associated with clinical symptoms and signs and radiologic, electrocardiographic, and physiologic features that permit proper differential diagnosis in most instances. The usual type of atrial septal defect, ostium secundum, is by far the most common form of interatrial communication, and it is one that can be repaired by several different satisfactory surgical technics. Ostium primum defects (partial form of common atrioventricular canal), total anomalous pulmonary venous connection, and common atrium are examples of less common forms of communication between the atria and require open cardiotomy with the use of extracorporeal circulation for satisfactory surgical treatment. Accuracy of diagnosis is, therefore, of practical importance for selection of patients for operation.

### Methods

Anatomic proof of the type of interatrial communication was obtained in 128 children at the Mayo Clinic either by surgical exploration (124) or at necropsy (4). Seventy-four patients had only ostium secundum defects, while 37 had ostium primum defects of the septum with associated clefts of the aortic leaflet of the mitral valves. Five patients among those who had ostium primum defects also had defects of the septal leaflet of the tricuspid valves. Twelve patients had either total anomalous pulmonary venous connection to the right atrium or a systemic vein that was draining into the right atrium. A common atrium was found in 5 patients, there being no remnant of atrial septal tissue, and the floor of the common atrium was formed by the fused septal leaflet of the tricuspid valve and aortic leaflet of the mitral valve.

All patients were studied by the usual clinical methods consisting of a carefully taken medical history, physical examination, roentgenogram of the thorax, and an electrocardiogram studied by vectorial analysis.[1] Cardiac catheterization* studies were obtained in 93 of the 128 patients (table 1).

### Results

The results in general are presented in tables 2, 3, and 4.

#### Ostium Secundum Defects

Patients with ostium secundum defects usually had no difficulties during infancy; only 4 of the 74 required surgical treatment before the age of 4 years because of recurrent pneumonia, retarded growth, or threatened cardiac decompensation. The remaining 70 patients in this group had mild symptoms or signs during childhood consisting of slight underdevelopment and minimal limitation of tolerance of exercise but no cyanosis.

All patients in this group had a systolic murmur in the second and third intercostal spaces at the left of the sternum. This murmur varied from a barely audible bruit with no accompanying thrill to a moderately intense murmur with a palpable thrill, the latter finding being uncommon but not rare.

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*Cardiac catheterization studies were performed by Drs. E. H. Wood and H. J. C. Swan, of the cardiovascular physiologic laboratories of the Mayo Clinic.

**Table 1**

*Interatrial Communications Proved by Surgical Exploration or Necropsy*

| Type | Cases, no. | Cardiac catheterization |
|---|---|---|
| Ostium secundum | 74 | 62 |
| Ostium primum | 37 | 18 |
| Common atrium | 5 | 5 |
| Total anomalous pulmonary venous connection | 12 | 8 |
| Totals | 128 | 93 |

**Table 2**

*Interatrial Communications: Gradations of Symptoms*

| Type | Mild | Severe | Cyanosis |
|---|---|---|---|
| Ostium secundum | + | — | — |
| Ostium primum | + | — | — |
| Common atrium | — | + | + |
| Total anomalous pulmonary venous connection | — | + | + |

**Table 3**

*Interatrial Communications: Nature of Electrocardiographic Data*

| Type | QRS | | Loop | |
|---|---|---|---|---|
| | Right axis | Left axis | Clockwise | Counterclockwise |
| Ostium secundum | + | — | + | — |
| Ostium primum | — | + | — | + |
| Common atrium | — | + | — | + |
| Total anomalous pulmonary venous connection | + | — | + | — |

**Table 4**

*Interatrial Communications: Oximetry and Cardiac Catheterization*

| Type | Oxygen desaturation | Pulmonary hypertension | Shunt | |
|---|---|---|---|---|
| | | | "Left-to-right" | "Right-to-left" |
| Ostium secundum | — | — | + | — |
| Ostium primum | — | — | + | — |
| Common atrium | + | + | + | + |
| Total anomalous pulmonary venous connection | + | ± | + | + |

occurring in 10 of 74 cases (14 per cent). An apical or midprecordial systolic murmur was noted in 15 cases, probably as a result of mitral (4) and tricuspid insufficiency (11). An almost universal sign was unusually wide, fixed splitting of the second cardiac sounds at the base of the heart, this feature being definite and readily distinguished from the narrow splitting of the second sounds in this area such as occurs normally in children. A middiastolic or late diastolic murmur was detected at the xiphoid area or inside the apex in the majority of patients as a result of "relative" tricuspid stenosis.

Mild to moderate cardiac enlargement, with prominence of the shadow of the main pulmonary artery, plus increased pulmonary vascular markings of varying degree, were the outstanding radiologic features (fig. 1).

Electrocardiographic evidence of diastolic overloading[2] of the right ventricle, often referred to as "incomplete right bundle-branch block" or "delayed activation of the right ventricle," was detected in all 74 patients (fig. 2). The diastolic overloading consisted of RSR′ complexes in leads taken from the right precordium. Vectorial analysis of the electrocardiograms revealed a clockwise rotation of the QRS loop in the frontal plane, with the major portion of the loop lying below the isoelectric point and the mean QRS axis ranging from +95 to +160 degrees in 71 cases (fig. 3), while in the remaining 3 patients the QRS loop was similar to that obtained from patients with common atrial ventricular canal with mean QRS axis ranging from −60 to −175 degrees (fig. 4), an incidence of 4 per cent.

Results of cardiac catheterization were available in 62 of the 74 patients. In all instances there was evidence of a left-to-right shunt at atrial level, while in 8 there was suggestive evidence of additional left-to-right flow in the right ventricle. Pulmonary arterial pressures were elevated above normal values in only 4 cases. There was no evidence of systemic arterial oxygen unsaturation.

**tium Primum Defects (Partial Form of Common rioventricular Canal)**[3, 4]

The medical history of the patients with is anomaly in most respects was similar to e history of patients with ostium secundum efects. Significant symptoms were recognized ring infancy in only 3 cases. Symptoms ising during childhood were, for the most rt, mild, consisting only of slight intoler- ce of exercise, and none of the patients had anosis (table 2).

A systolic murmur of varying intensity in e pulmonary area was detected in all cases. n addition, an apical systolic murmur was resent in many children of this group, al- hough it was often difficult to be certain that his was a separate or different murmur rather than an extension of the pulmonic murmur. Wide splitting of the second cardiac sounds at the base was noted in many instances but, in general, it was less pronounced than in patients with ostium secundum defects.

Radiologic examination revealed slight to moderate cardiac enlargement in all instances, and pulmonary vascular markings were increased.

The electrocardiograms of these patients revealed evidence of diastolic overloading of the right ventricle in most but not all instances (fig. 5). There was evidence of diastolic overloading of the left ventricle in many patients. Abnormal P waves suggesting enlargement of the atrium were observed commonly. The most striking characteristic of patients with ostium primum defects was the type of QRS loop in the frontal plane. In all patients this loop rotated in a counterclockwise direction, with the major portion of the loop superior to the isoelectric point (32 cases), or described a figure-of-8 along the horizontal line with the initial part of the loop rotating in a counterclockwise direction (5 cases) (fig. 4). The mean QRS axis ranged from −60 to + −180 degrees. The terminal QRS vector invariably was located between 0 and + −180 degrees.

Results of cardiac catheterization indicated left-to-right shunt at atrial level in all in-

**Figure 1**

*Ostium secundum defect of the atrial septum. The patient was 5 years old. Moderate cardiac enlargement and increased pulmonary vascular shadows.*

stances (18 cases studied), with suggestive evidence of additional left-to-right shunt in the right ventricle in 4 cases. Pulmonary arterial pressures were normal or only slightly elevated in all patients of this group. There was no evidence of systemic arterial oxygen unsaturation.

**Common Atrium**[5]

Symptoms were present in all 5 patients in this group during infancy and early childhood. Recurrent infections of the respiratory tract and pneumonia during the first year of life occurred in 4 of the 5 children. Each patient was reported to have had cyanosis in the past, transient in 2 but fairly constant in the other 3. Physical signs were somewhat variable in this group. All had moderate systolic murmurs in the pulmonic area, with wide extension over the precordium and toward the left axilla, and 2 had rather prominent diastolic murmurs along the lower left border of the sternum. The second heart sounds in the pulmonic area were widely split in all, but in 2 there was considerable accentuation of the second component of the sound in the

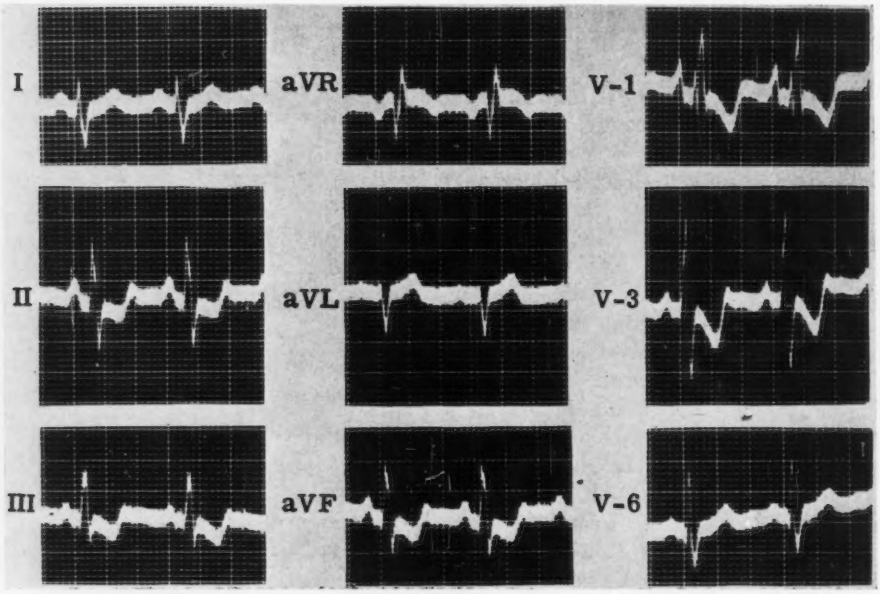


**Figure 2**

*Ostium secundum defect of the atrial septum. The patient was 4 years old. RSR′ complexes in lead $V_1$ interpreted as evidence of diastolic overloading of the right ventricle. Right axis deviation (+110 degrees) and the QRS loop rotates in a clockwise direction (see fig. 3).*

pulmonic area, with an associated palpable shock on the thoracic wall indicative of pulmonary hypertension.

Considerable cardiac enlargement was demonstrated by radiologic examination in all 5 cases, and pulmonary vascular markings were considerably increased (fig. 6).

Electrocardiographic studies revealed evidence of diastolic overloading of the right ventricle in 2 cases and combined systolic and diastolic overloading of the right ventricle in the other 3. There was suggestive evidence of left ventricular overloading in 2 of the 5 cases. In all 5 patients analysis of the QRS vectors revealed QRS loops in the frontal plane that were identical in configuration with those described for ostium primum defects (fig. 4). The mean QRS axis varied from −60 to −160 degrees.

Studies of cardiac catheterization showed pulmonary hypertension to be severe in 2 patients, moderate in 2, and normal in the remaining patient. There was evidence of left-to-right flow in the right atrium, and the oxygen saturation of pulmonary arterial blood was equal to, or slightly higher than, the saturation of systemic arterial blood, the systemic saturation ranging from 83 to 92 per cent. Indicator-dilution curves after injection of the medium into the right atrium and vena cava were identical and indicated a "right-to-left" shunt at atrial level, while curves charted from the right ventricle and pulmonary artery were identical and indicative of a "left-to-right" shunt. These findings are diagnostic of a common mixing chamber at atrial level.

**Total Anomalous Pulmonary Venous Connection**

Severe symptoms occurred during early infancy in 7 of the 12 patients with total anomalous pulmonary venous connection in this series. Four died of cardiac failure before the age of 4 months, in spite of medical treatment, and 3 had intractable cardiac fa-

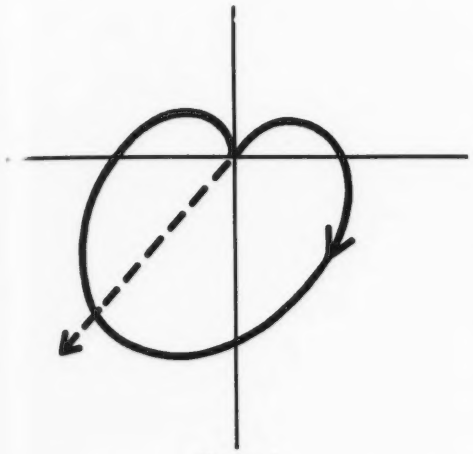

**Figure 3**

*Characteristic QRS loop in the frontal plane obtained from vectorial analysis of the scalar electrocardiogram of patients with ostium secundum defects of the atrial septum and total anomalous pulmonary venous connection. There are clockwise rotation, with the major portion of the loop lying inferior to the isoelectric point, and right axis deviation.*

ure that necessitated surgical treatment during the first year of life. The other 5 patients experienced moderate difficulty during infancy, but during childhood had only slight symptoms and were not particularly different from patients with other forms of interatrial communications, with the exception of transient cyanosis usually detectable after exertion.

Murmurs were variable, but in most instances a soft to moderate systolic murmur was noted in the pulmonic area. In 3 of the infants no cardiac murmurs were detected. The second sound in the pulmonic area was accentuated in 10 of the 12 cases.

Moderate cardiac enlargement and increased pulmonary vascular markings were characteristics of radiologic examinations in all patients with this type of communication. Four patients had prominent supracardiac shadows described as virtually pathognomonic of anomalous pulmonary venous connection to the superior vena cava or left innominate vein (fig. 7).

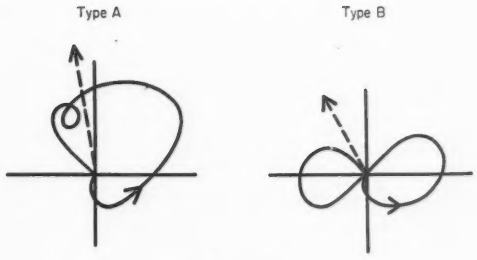


**Figure 4**

*Characteristic QRS loops in the frontal plane obtained from vectorial analysis of the electrocardiogram of patients with ostium primum defects of the atrial septum (partial form of common atrioventricular canal). A counterclockwise rotation is seen, with the major portion of the loop superior to the isoelectric point (A) or a figure-of-8 loop along the horizontal line, with the first portion rotating in a counterclockwise direction (B).*

Electrocardiograms revealed diastolic overloading patterns of the right ventricle in 9 of the 12 patients in the group, but there was additional evidence of elevated right ventricular pressure in 5 of these 9. The remaining 3 patients exhibited only the electrocardiographic characteristics of systolic overloading of the right ventricle. qR complexes in lead $V_1$ were present in 4 cases. Abnormal P waves indicative of right atrial enlargement were present in 10 of the 12. QRS loops in the frontal plane all were directed in a clockwise direction, with the major portion of the loop below the isoelectric point and with the mean QRS axis ranging from +90 to +130 degrees (fig. 3), hence identical to the loops described in ostium secundum defects. The P-R interval was prolonged in 1 patient.

Results of cardiac catheterization were available in 8 of the 12 patients. Pulmonary hypertension was noted in 6. Four had systolic pulmonary arterial pressures equal to the systemic pressure, while the other 2 had pulmonary arterial systolic pressures of approximately 50 per cent of the systemic pressure. Studies of oxygen saturation revealed left-to-right shunt in the right atrium or superior vena cava in all cases, and pulmonary arterial blood saturation was equal to, or slightly greater than, that of systemic arte-

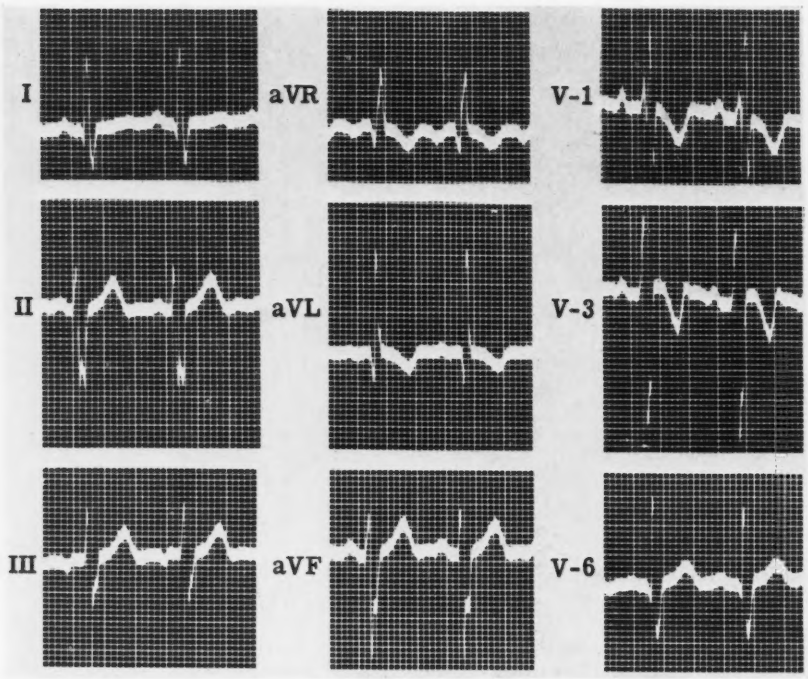


**Figure 5**

*Ostium primum defect of the atrial septum (partial form of common atrioventricular canal). The patient was 2 years old. RSR′ complexes in lead $V_1$ indicate diastolic overloading of the right ventricle. There is left axis deviation (−120 degrees) and the QRS loop rotates in a counterclockwise direction (see fig. 4A).*

rial blood in all cases. Indicator-dilution curves were identical to those described for common atrium. Ear oximetry was carried out in 7 patients, all showing unsaturation with a range from 68 to 91 per cent.

## Discussion

The four types of interatrial communication concerned herein had many features common to all, as well as significant differences (table 5). Moderate to severe symptoms were noted during infancy in the patients with total anomalous pulmonary venous connection and common atrium. The medical histories of patients with ostium secundum and ostium primum defects were similar in that they generally disclosed minimal symptoms. Patients with common atrium and total anomalous pulmonary venous connection had transient or persistent cyanosis, while those with ostium secundum and ostium primum defects did not. Systolic murmurs in the pulmonic area were noted in all, but additional apical systolic murmurs suggesting mitral insufficiency were found in many of the patients with ostium primum defects. Cardiac enlargement and prominent pulmonary vascular markings were demonstrated in all cases by radiologic examination with no differential features except

**Table 5**

*Interatrial Communications: Differential Diagnosis*

| Type | Cyanosis | QRS loop | |
|---|---|---|---|
| | | Clockwise | Counter-clockwise |
| Ostium secundum | — | + | — |
| Ostium primum | — | — | + |
| Common atrium | + | — | + |
| Total anomalous pulmonary venous connection | + | + | — |

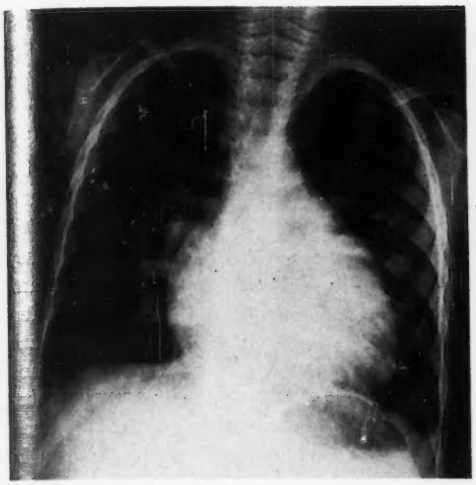

**Figure 6**

*Common atrium. The patient was 3 years old. Marked cardiac enlargement and increased pulmonary vascular shadows are seen.*

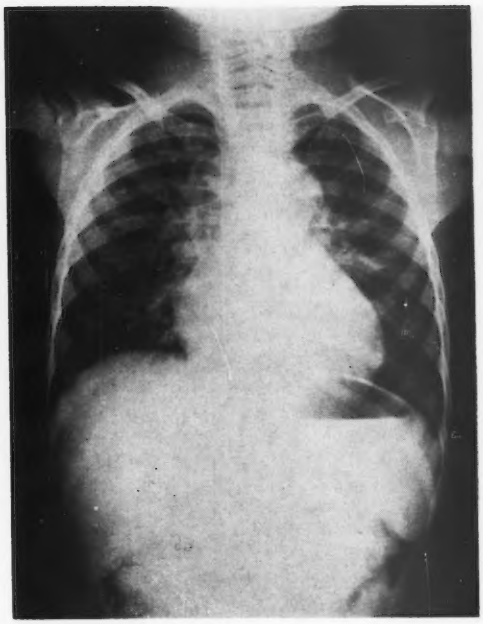

**Figure 7**

*Total anomalous pulmonary venous connection to the left innominate vein. The patient was 6 years old. The prominent supracardiac shadow in association with the cardiac silhouette produces a "figure-of-8" configuration pathognomonic of this condition.*

for a prominent supracardiac shadow in 4 patients who had total anomalous pulmonary venous connection, a finding which is virtually pathognomonic of this condition if the connection is to the left innominate vein or superior vena cava.

Results of cardiac catheterization are virtually identical among patients with ostium secundum and ostium primum defects, showing a left-to-right shunt at atrial level. Occasionally, the position of the catheter extending from the right to the left atrium will suggest the location of the septal defect, but this is rarely conclusive. Results of physiologic studies of patients with common atrium and total anomalous pulmonary venous connection are identical, showing evidence of a common mixing chamber at atrial level, and indicating that the oxygen saturation of the blood in the pulmonary artery is equal to, or slightly greater than, that of the blood in the systemic arteries. Thus, it is apparent that the results of cardiac catheterization readily distinguish patients with ostium secundum and ostium primum defects from those with common atrium and total anomalous pulmonary venous connection, but cannot be relied upon to distinguish patients with ostium secundum from those with ostium primum or patients with common atrium from those who have total anomalous pulmonary venous connection.

Vectorial electrocardiographic analysis has proved to be of great value in contributing to accurate differential diagnosis of these conditions. The QRS vectors in the frontal plane described a counterclockwise loop above the isoelectric point, or a figure-of-8 along the horizontal line in all cases of ostium primum defects and common atrium. This QRS loop was clockwise and below the isoelectric point in all patients with total anomalous pulmonary venous connection and in 96 per cent of patients with ostium secundum defects.

By combining the clinical history and the results of physical examination, radiologic study, electrocardiographic analysis, and car-

**Table 6**

*Interatrial Communications: Accuracy of Diagnosis*

| Condition | Cases, no. | Correct diagnosis, cases |
|---|---|---|
| Ostium secundum | 74 | 71 |
| Ostium primum | 37 | 37 |
| Totals | 111 | 108 |

**Table 7**

*Interatrial Communications: Results of Surgical Treatment*

| Defect, type | Cases, no. | Operated upon | Deaths | Per cent |
|---|---|---|---|---|
| Ostium secundum | 74 | 74 | 0 | 0 |
| Ostium primum | 37 | 37 | 2 | 5 |
| Common atrium | 5 | 5 | 1 | 20 |
| Total anomalous pulmonary venous connection | 12 | 8 | 4 | 50 |
| Totals | 128 | 124 | 7 | 5 |

diac catheterization, an accurate diagnosis was possible in all but 6 of the 128 patients in this series. The proper diagnosis was not made in 3 infants with total anomalous pulmonary venous connection, aged 9 days, 6 weeks, and 4 months, respectively, who were virtually moribund at the time of admission to the hospital and who died within a few hours after the initial examination. The condition of the 3 patients with ostium secundum defects who had QRS loops of the common atrioventricular-canal type also was improperly diagnosed as ostium primum defect.

It is evident that patients with ostium secundum and ostium primum defects have many features in common with regard to symptoms, signs, roentgenologic findings, and results of physiologic studies, but the electrocardiograms differed in important respects and allowed accurate distinction to be made in 97 per cent of the 111 children with ostium secundum and ostium primum defects in this series (table 6). The practical importance of this differentiation is evident if ostium secundum defects are to be repaired by technics other than open cardiotomy.

Errors in diagnosis were made in 3 of 74 patients with ostium secundum defects (4 per cent), and these patients were operated upon by means of extracorporeal circulation, thus posing no particular problem to the surgeon. On the other hand, no patients with ostium primum defects were scheduled for operation under a mistaken diagnosis, since all had the characteristic electrocardiographic features mentioned.

Patients with total anomalous pulmonary venous connection and common atrium manifested similar clinical and physiologic features but entirely different QRS loops and vectors in the electrocardiograms in this series, and thus were readily distinguished, one from another, by this means. All the patients of these 2 categories were operated upon by means of open cardiotomy except for the 4 previously mentioned infants with total anomalous pulmonary venous connection who died shortly after admission to the hospital.

A history of cyanosis in the past and the presence of cyanosis at the time of examination in patients with these 2 lesions (total anomalous pulmonary venous connection and common atrium) warrant special mention. If the presence of the usual type of interatrial communication is suspected initially in such an instance, the suspicion of an inoperable lesion might be entertained. The evidence of increased pulmonary blood flow in roentgenograms of the thorax should alert the clinician, however, to the possibility of a common mixing chamber leading to systemic arterial oxygen desaturation in the presence of an increased pulmonary blood flow.

Surgical repair was accomplished for 124 of the 128 patients in this series, the exception being the afore-mentioned 4 infants (table 7). Among the 74 patients who had ostium secundum defects there were no deaths; among the 37 patients with ostium primum defects who were operated upon there were 2 deaths; among the 8 patients with total anomalous pulmonary venous connection who were operated upon there were 4 deaths, and among the 5 patients with common atrium who were operated upon there was 1 death.

### Summary

Of 128 children with anatomically confirmed interatrial communications 74 had ostium secundum, 37 had ostium primum defects, 5 had common atrium, and 12 had total anomalous pulmonary venous connection.

Analysis of the medical history, physical examination, roentgenogram, and electrocardiogram resulted in accurate diagnosis in most instances. In 6 of the 128 patients the proper diagnosis was not made: 3 infants with total anomalous pulmonary venous connection died within a few hours after admission to the hospital and did not have proper diagnostic evaluation; the condition of 3 other patients with ostium secundum defects was misdiagnosed as ostium primum defect before surgical treatment.

In patients with ostium secundum and ostium primum defects the symptoms, signs, roentgenologic data, and findings at cardiac catheterization are similar, but differences in respect to the electrocardiograms are striking when the latter are subjected to vèctorial analysis. The QRS loop is clockwise in the presence of ostium secundum defect and counterclockwise when ostium primum defect is at hand.

Clinical and roentgenologic manifestations also are noted among patients with common atrium and total anomalous pulmonary venous connection, and the findings at cardiac catheterization likewise may be similar, but the electrocardiographic differences are significant. The QRS loop is counterclockwise in patients with common atrium and clockwise in patients with total anomalous pulmonary venous connection.

### Summario in Interlingua

Inter 128 juvenes con anatomicamente confirmate communication interatrial, 74 habeva ostio secunde, 37 ostio prime, 5 atrio commun, e 12 total anormalitate de connexion pulmono-venose.

Le analyse del historia medical, del examine physic, del roentgenogramma, e del electrocardiogramma resultava in le correcte diagnose in le majoritate del casos. In 6 del 128 casos, le correcte, diagnose non esseva trovate per iste medios. Tres infantes con total anormalitate del connexion pulmono-venose moriva intra alicun horas post lor admission al hospital e non recipeva un adequate evalutation diagnostic. Le condition de 3 altere patientes con ostio secunde esseva maldiagnosticate como ostio prime ante le intervention chirurgic.

In patientes con defectos del typo de ostio secunde e de ostio prime, le symptomas, le signos, le datos roentgenologic, e le constatationes del catheterismo cardiac es simile, sed differentias electrocardiographic deveni frappante quando le electrocardiogrammas es es subjicite a un analyse vectorial. Le ansa de QRS exhibi un direction dextrorse in le presentia de ostio secunde e un direction sinistrorse in le presentia de ostio prime.

Manifestationes clinic e roentgenologic occurrente tanto in patientes con atrio commun como etiam in patientes con total anormalitate del connexion pulmono-venose es similemente notate. In tal casos il occurre etiam identitate del constatationes de catheterismo cardiac, sed le differentias vecto-cardiographic es de novo significative. Le ansa QRS ha un direction sinistrorse in patientes con atrio commun e dextrorse in patientes con total anormalitate del connexion pulmono-venose.


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# Some Effects of Digoxin upon the Heart and Circulation in Man

## Digoxin in Combined (Left and Right) Ventricular Failure

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HEMODYNAMIC studies of the effects of cardiac glycosides on the failing human heart have been numerous and have shown one consistent alteration following administration of the drug, namely, a rise in cardiac output.[1-13] Alterations in lesser circulation pressures have not always been homogeneous. However, they are more or less predictable in failure of only one ventricle. When only the left ventricle fails and a sinus mechanism is present, a decrease in the elevated pulmonary artery pressures occurs after the administration of Digoxin and the normal right ventricular diastolic pressure shows no change.[5, 14] In isolated right ventricular failure with this rhythm the elevated right ventricular diastolic pressure falls and pulmonary artery systolic pressure tends to rise rather than to decline.[7, 15, 16] In the presence of combined ventricular failure, the behavior of these pressures has been variable.[4, 6, 8, 9, 11, 12, 17] The reasons for this lack of uniformity may well be due to the presence of a number of physiologic variables, which are complications of the state of failure but which nonetheless may influence the response of the circulation to drugs.

It is the purpose of this investigation to examine the various factors influencing the response of combined left and right ventricular failure to Digoxin. Because mechanical factors such as valvular or pericardial lesions may of themselves alter pressure patterns, patients with such lesions were excluded from this presentation. It also seemed wise to group patients according to basic cardiac rhythm, since it is known that the atrial arrhythmias influence the hemodynamic picture to some extent.[12]

### Materials and Methods

Thirteen patients with hypertensive and/or arteriosclerotic heart disease were studied with use of the technic of cardiac catheterization. The methods utilized in this laboratory to measure blood pressures, cardiac output (by the Fick principle), and blood volume have been published previously.[5, 8] The stroke volume was calculated by dividing the cardiac output by the ventricular rate. The pulse pressure was determined by the difference between the average systolic and average diastolic pressures, which were measured over 2 respiratory cycles in patients with sinus rhythm and 2 or more complete cycles in those with atrial fibrillation in order to sample at least 10 consecutive beats. It is recognized that in atrial fibrillation the values for stroke volume and pulse pressure are approximate. The detailed protocol and the criteria used for evaluating significant change following the drug are the same as in previous reports.[5, 7] Although several determinations of pressures were made in the control period, only one representative value is given in tables 1, 2, and 3. Following administration of the drug, pressure measurements were made every 5 to 15 minutes; however, for the sake of brevity, only the values nearest in time to the determination of cardiac output appear in the tables.

All patients had clinical evidence of marked pulmonary and peripheral congestion and were classified as IV-D at the time of study according to the

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*National Heart Institute Trainee of the National Institutes of Health.

eria of the New York Heart Association. The patients are grouped in tables 1 and 2 according to the presence of sinus rhythm or atrial fibrillation. Details of diagnoses can be found in these tables as can the dosage of Digoxin administered. Of those with sinus rhythm, 1 (no. 625) had had symptoms of failure for 3 years and was the most disabled of this group. The duration of complaints was much shorter in the 4 others in table 1, ranging from 1 to 6 months. Two (nos. 417 and 625) had had infrequent mercurial diuretics but none of the 5 had ever received digitalis bodies. One man (no. 519) had needed 3 thoracenteses on the left but had reaccumulated pleural fluid before his catheterization. In the group with atrial fibrillation, 3 (nos. 588, 682, and 794) had had previous episodes of failure for which they had been digitalized. They had discontinued the medication, however, 6 weeks, 4 months, and 5 months, respectively, before the study. Symptoms of failure recurred almost immediately in 1 man (no. 682). In the other 2 (nos. 588 and 794) as well as in the remaining 5 who were never digitalized, the symptoms had been present for less than 1 month prior to admission to the hospital. Two subjects (nos. 453 and 794) had received 1 or 2 doses of mercurial diuretics and in 5 (nos. 453, 806, 544, 794 and 940) thoracenteses were required to alleviate severe orthopnea but chest fluid was present at the time of study, as indicated in table 2.

It is of interest that in the group of patients with sinus rhythm the symptoms of left ventricular failure preceded those of peripheral congestion by a considerable period of time, while those individuals with atrial fibrillation complained of symptoms of right ventricular failure very shortly after those of left-sided failure had appeared.

## Results

### Patients with Combined Left and Right Ventricular Failure and Sinus Rhythm

Prior to administration of Digoxin the cardiac output in 4 of the 5 patients (table 1) was lower than normal and there was moderate to severe pulmonary hypertension with a wide pulse pressure and an elevated right ventricular diastolic pressure. Total blood volume was increased in all 5 subjects. The plasma volume was normal only in the 1 patient (no. 417) who had had repeated diuretics. The ventilation was also elevated in all 5 but the oxygen uptake was within normal limits. Mild to moderate arterial blood oxygen unsaturation (93 to 85 per cent) occurred in 4 subjects.

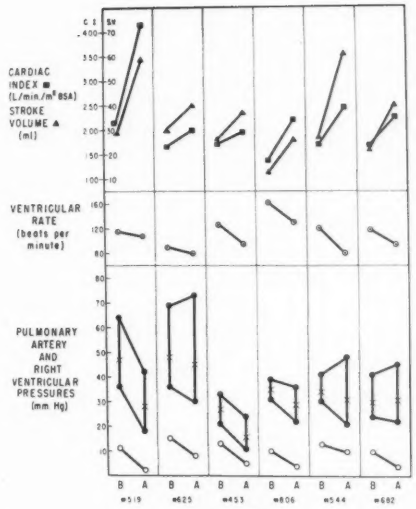
CARDIAC INDEX ■ (L/min./m² BSA)
STROKE VOLUME ▲ (ml)
VENTRICULAR RATE (beats per minute)
PULMONARY ARTERY AND RIGHT VENTRICULAR PRESSURES (mm Hg)
B A B A B A B A B A B A
#519 #625 #453 #806 #544 #682

**Figure 1**

*Hemodynamic responses to the acute administration of Digoxin in patients with left and right ventricular failure. The symbols are identified as follows: the square indicates the cardiac index; the triangle, the stroke volume; the target dot, the ventricular rate; the solid circles, the systolic and diastolic pulmonary artery pressures; the open circles, the right ventricular end-diastolic pressures; and the cross, the pulmonary artery mean pressures. B represents values before and A values after Digoxin. Patients 519 and 625 were in sinus rhythm and the remaining 4 were in atrial fibrillation.*

After Digoxin was given (via the catheter) the cardiac output rose in all patients (9 to 94 per cent) as did the stroke output. The heart rate fell in all, although hardly in a striking fashion (from 3 to 15 beats per minute). The changes in systemic arterial pressures were not great although there was a tendency to an increase in the systolic level with little or no fluctuation in diastolic or mean pressure. The right ventricular diastolic pressure declined in all 5 patients.

In 3 of the 4 patients in whom measurements of pulmonary arterial pressures were available, the systolic, diastolic, mean and pulse pressures decreased (as exemplified by no. 519 in figure 1) while in the fourth (no. 625) the significant changes were a fall in diastolic and a rise in pulmonary artery pulse pressure (fig. 1). In this fourth case a second

**Table 1**

*Hemodynamic Data in Five Patients in Combined Left and Right Ventricular Failure with Sinus Rhythm before and after Administration of Digoxin*

| Case, age sex, BSA | Diagnosis | Time | Ventricular rate (beats/min.) | Cardiac index (L./min./M.² BSA) | Stroke volume (ml.) | Oxygen uptake (ml./min./M.² BSA) | Ventilation (L./Min./M.² BSA) | A-V oxygen diff. (vol. %) | Arterial blood: Oxygen cont. (vol. %) | Arterial blood: Oxygen sat. (%) | Pressures in mm. Hg: Systemic artery s/d (mean) | Pressures in mm. Hg: Pulmonary artery s/d (mean) | Pressures in mm. Hg: Right ventricle d | TBV (ml./M.² BSA) | PV (ml./M.² BSA) | Hematocrit (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| #519, 38M, 1.55 | HCVD, EH, chr. pyelonephr. gallop, puls. alt., lt. hydrothorax | Control | 115 | 2.15 | 29 | 144 | 5.61 | 6.7 | 15.6 | 92 | 212/132 (162) | 64/36 (47) | 11 | 3340 | 1940 | 42 |
| | | 34* | 100 | 3.95 (+83%) | 61 | 150 | 5.73 | 3.8 | 14.7 | 88 | 202/111 (142) | 40/17 (26) | — | | | |
| | | 62 | 109 | 4.18 (+94%) | 59 | 154 | 6.23 | 3.7 | 14.8 | 90 | 226/121 (158) | 42/18 (28) | 2 | | | |
| #616, 32M, 1.83 | HCVD, EH, gallop, puls. alt. bilat. hydrothorax | Control | 93 | 2.56 | 48 | 161 | 5.81 | 6.3 | 12.4 | 96 | 173/123 (140) | 56/25 (39) | 10 | 3237 | 2145 | 33 |
| | | 16† | 87 | 3.39 (+33%) | 71 | 152 | 5.52 | 4.5 | 12.4 | 96 | 196/121 (149) | 40/18 (27) | 2 | | | |
| | | 38 | 78 | 3.21 (+25%) | 75 | 147 | 5.82 | 4.6 | 12.4 | 96 | 198/119 (152) | 24/6 (14) | 1 | | | |
| #919, 67F, 1.58 | HCVD, EH, calc. aorta, diabetes, K-W nephr., bilat. hydrothorax | Control | 71 | 2.82 | 60 | 138 | 4.79 | 4.9 | 13.8 | 85 | 261/95 (159) | 67/18 (37) | 8 | 3668 | 2217 | 39 |
| | | 30* | 68 | 2.79 | 65 | 137 | 4.67 | 4.9 | 13.2 | 81 | 276/90 (159) | 67/15 (35) | 5 | | | |
| | | 41 | 68 | 3.06 (+ 9%) | 71 | 138 | 4.67 | 4.5 | 13.3 | 83 | 261/79 (146) | 53/12 (25) | 3 | | | |
| #417, 77M, 1.47 | ASHD, EH, CS, MF, old myo. infarct, APC, angina | Control | 85 | 2.18 | 38 | 139 | 4.66 | 6.4 | 19.9 | 93 | 145/78 (103) | 40/18 (22) | 9 | 3510 | 1650 | 53 |
| | | 23* | 84 | 2.22 | 39 | 137 | 4.69 | 6.2 | 19.3 | 96 | 165/73 (112) | 36/— (—) | 1 | | | |
| | | 53 | 79 | 2.47 (+13%) | 46 | 131 | 4.11 | 5.3 | 18.6 | 93 | 174/82 (115) | 29/— (—) | 2 | | | |
| #625, 57M, 1.61 | HCVD, ASHD, EH, CS, MF, LBBB, gallop | Control | 90 | 1.67 | 30 | 135 | 5.93 | 8.1 | 14.6 | 97 | 166/108 (128) | 69/36 (48) | 15 | 3890 | 2330 | 40 |
| | | 29† | 79 | 1.94 (+16%) | 39 | 130 | 5.29 | 6.7 | 13.9 | 95 | 180/99 (127) | 73/33 (47) | 11 | | | |
| | | 55 | 80 | 1.99 (+19%) | 40 | 127 | 5.78 | 6.4 | 14.4 | 98 | 185/99 (130) | 73/30 (45) | 8 | | | |
| | | 19‡ | 94 | 2.17 | 37 | 130 | 5.31 | 6.0 | 15.0 | 97 | 141/87 (106) | 32/17 (24) | 1 | 3775 | 2250 | 41 |

*Minutes after 1.0 mg. Digoxin via catheter.

†Minutes after 1.25 mg. Digoxin via catheter.

‡Second study 19 days after acute Digoxin study.

ASHD, arteriosclerotic heart disease; AF, atrial fibrillation; APC, atrial premature contractions; BSA, body surface area; CS, coronary sclerosis; EH, enlarged heart; HCVD, hypertensive cardiovascular disease; K-W nephr., Kimmelstiel-Wilson nephrosis; LBBB, left bundle-branch block; MF, myocardial fibrosis; NST, normal sinus tachycardia; PV, plasma volume; Puls. Alts., plusus alternans; TBV, total blood volume; VPC, ventricular premature contractions.

study was made 19 days after the first, at which time he was no longer considered clinically to be in failure. The second catheterization (table 1) revealed a cardiac output which was higher than the final post-Digoxin value in the first study, a striking decrease in all pulmonary artery pressures, a further drop in right ventricular diastolic pressure, and no change in the large blood volume. None of the subjects in this group with sinus rhythm had any change in ventilation after Digoxin.

**Patients with Combined Left and Right Ventricular Failure and Atrial Fibrillation**

The level of blood flow in these 8 individuals was markedly reduced (table 2) with a cardiac index of less than 2.0 liters in every instance. In each there was elevation of all lesser circulation pressures but the level of pulmonary hypertension was quite different from that of the group with sinus rhythm; the systolic and pulse pressures were much lower. Tricuspid insufficiency was present in all 8 patients as judged from the right atrial pressure curves. Total blood volume was universally increased and the only subject with a normal plasma volume (no. 453) had had several doses of mercurial diuretics. In this group too, ventilation was increased but the oxygen uptake was within normal limits. Mild arterial oxygen unsaturation (92 to 93 per cent) occurred in 3 subjects.

After administration of Digoxin the cardiac output increased, 13 to 73 per cent, and the ventricular rate declined to a greater extent than in the group with sinus rhythm. There were also large increases in stroke volume. The changes in systemic arterial pressures were the same as in the group with sinus rhythm. The right ventricular diastolic pressure fell in the 7 instances in which it was measured.

The alterations in the pulmonary arterial pressures produced by the drug in these 8 subjects can be divided into 2 types. In the first, as seen in 3 patients (nos. 453, 806, and 544), the diastolic pressure fell after Digoxin but the systolic response was variable, falling (no. 453), remaining the same (no. 806), and rising (no. 544) (fig. 1). In all, the pulse pressure rose. In the second type, as occurred in 5 patients (and as is exemplified by no. 682 in fig. 1) there were minor pressure changes in the pulmonary artery systolic and diastolic pressures but the pulse pressures increased in 4 of the 5 during the period observed. In the fifth (no. 794) the pulse pressure remained unchanged. Ventilation did not alter after Digoxin in any of these patients.

Fortunately, it was possible to restudy 4 of these 8 patients (nos. 544, 588, 682, and 794) when clinical evidences of congestive failure had disappeared. All lesser circuit pressures were lower at this later date even though blood flows were approximately in the same range as on the first study (table 2). The blood volumes were also considerably lower although not one was normal. The ventilation remained unchanged at the time of the second evaluation, despite the improvements in the circulation.

## Discussion

**Hemodynamic Considerations**

As was expected, the inotropic effect of the drug was expressed by a rise in cardiac output in all 13 subjects. Heart rate decreased in all and contributed to the accompanying increase in stroke volume. The average increase in stroke output in the patients with atrial fibrillation was 77 per cent as compared to 46 per cent in those with sinus rhythm. The effect on ventricular rate was much greater (an average decline of 28 beats per minute) in those with atrial fibrillation than in those with sinus rhythm (8 beats per minute). Heart rate, however, and output did not always vary in a consistent manner, as there were large increases in blood flow with only small changes in rate (no. 519, table 1) and large falls in rate with less impressive rises in output (no. 453, table 2). There was no fixed relationship in time between changes in ventricular rate and cardiac output. In some patients (nos. 544 and 940, table 2) there was a progressive fall in the heart rate and a continuing rise in output, while in others the ven-

**Table 2**

*Hemodynamic Data in Eight Patients in Combined Left and Right Ventricular Failure with Atrial Fibrillation before and after Administration of Digoxin*

| Case, age sex, BSA | Diagnosis | Time | Ventricular rate (beats/min.) | Cardiac index (L./min./M.² BSA) | Stroke volume (ml.) | Oxygen uptake (ml./min./M.² BSA) | Ventilation (L./Min./M.² BSA) | A-V oxygen diff. (vol. %) | Arterial blood: Oxygen cont. (vol. %) | Arterial blood: Oxygen sat. (%) | Pressures in mm. Hg: Systemic artery s/d (mean) | Pressures in mm. Hg: Pulmonary artery s/d (mean) | Pressures in mm. Hg: Right ventricle d | TBV (ml./M.² BSA) | PV (ml./M.² BSA) | Hematocrit (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| #453, 69M, 1.81 | ASHD, EH, CS, MF, AF, rt. hydrothorax | Control | 126 | 1.71 | 25 | 120 | 6.4 | 7.0 | 20.6 | 94 | 136/87 (106) | 33/21 (27) | 13 | 3120 | 1430 | 54 |
| | | 32* | 100 | 1.71 | 31 | 115 | 6.0 | 6.7 | 20.7 | 95 | 146/83 (105) | 25/13 (18) | 7 | | | |
| | | 64 | 95 | 1.95 (+13%) | 37 | 120 | 6.4 | 6.2 | 20.4 | 94 | 143/83 ( 96) | 24/11 (16) | 5 | | | |
| #806, 62M, 1.53 | ASHD, EH, CS, MF, AF, VPC, bilat. hydrothorax | Control | 163 | 1.33 | 13 | 137 | 7.13 | 10.3 | 17.9 | 94 | 102/74 ( 83) | 39/31 (35) | 10 | 3297 | 1763 | 47 |
| | | 24‡ | 128 | 1.84 (+38%) | 22 | 144 | 6.66 | 7.8 | 17.0 | 94 | 115/82 ( 95) | 38/26 (31) | 7 | | | |
| | | 56 | 130 | 2.21 (+66%) | 26 | 144 | 6.73 | 6.5 | 16.7 | 92 | 122/82 ( 97) | 36/22 (29) | 4 | | | |
| #544, 58M, 1.88 | ASHD, EH, CS, MF, AF, bilat. hydrothorax | Control | 120 | 1.70 | 27 | 128 | 5.75 | 7.5 | 18.6 | 94 | 118/87 ( 97) | 41/30 (34) | 13 | 6620 | 3320 | 50 |
| | | 14* | 90 | 2.07 (+22%) | 43 | 132 | 5.80 | 6.4 | 17.7 | 92 | 136/89 (107) | 49/26 (34) | 12 | | | |
| | | 33 | 80 | 2.45 (+44%) | 61 | 130 | 5.80 | 5.3 | 17.9 | 96 | 142/83 (100) | 48/21 (31) | 10 | | | |
| 1.73 | | 12§ | 60 | 3.09 | 86 | 167 | 6.45 | 5.4 | 22.1 | 96 | 135/72 ( 95) | 27/9 (17) | 2 | 4288 | 1948 | 55 |
| #588, 67M, 1.62 | ASHD, EH, CS, MF, AF, bilat. hydrothorax | Control | 124 | 1.90 | 25 | 131 | 5.30 | 6.9 | 18.3 | 93 | 136/83 (104) | 30/18 (23) | 8 | 4540 | 2220 | 42 |
| | | 22† | 107 | 1.86 | 28 | 136 | 5.83 | 7.3 | 18.8 | 95 | 161/95 (117) | 33/19 (24) | 8 | | | |
| | | 46 | 102 | 2.18 (+15%) | 35 | 144 | 6.09 | 6.6 | 18.9 | 94 | 172/96 (125) | 35/18 (24) | 6 | | | |
| | | 65 | 100 | 2.83 (+49%) | 46 | 138 | 6.12 | 4.9 | 17.8 | 90 | 170/88 (119) | 31/14 (21) | 4 | | | |
| 1.58 | | 22§ | 80 | 2.25 | 44 | 115 | 4.61 | 5.1 | 18.1 | 92 | 148/81 (116) | 20/11 (13) | 3 | 3868 | 1920 | 50 |

Table 2 (Continued)

| Case, age sex, BSA | Diagnosis | Time | Ventricular rate (beats/min.) | Cardiac index (L./min./M.² BSA) | Stroke volume (ml.) | Oxygen uptake (ml./min./M.² BSA) | Ventilation (L./Min./M.² BSA) | A-V oxygen diff. (vol. %) | Arterial blood: Oxygen cont. (vol. %) | Arterial blood: Oxygen sat. (%) | Pressures in mm. Hg: Systemic artery s/d (mean) | Pressures in mm. Hg: Pulmonary artery s/d (mean) | Right ventricle d | TBV (ml./M.² BSA) | PV (ml./M.² BSA) | Hematocrit (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| #437, 65M, 1.82 | HCVD, ASHD, EH, CS, MF, AF | Control | 129 | 1.56 | 22 | 134 | 6.1 | 8.7 | 18.6 | 93 | 149/106 (123) | 26/13 (19) | 8 | 4040 | 2090 | 48 |
| | | 18* | 111 | 1.99 (+28%) | 33 | 144 | 5.6 | 7.3 | 17.1 | 91 | 165/97 (122) | 28/16 (18) | — | | | |
| | | 57 | 111 | 2.48 (+59%) | 41 | 141 | 4.0 | 5.7 | 17.4 | 94 | 161/86 (112) | 29/14 (19) | 5 | | | |
| | | 71 | 90 | 2.69 (+73%) | 55 | 143 | 5.8 | 5.3 | 16.5 | 93 | 173/91 (121) | 30/12 (20) | 3 | | | |
| #682, 68M, 1.65 | ASHD, EH, CS, MF, AF, VPC | Control | 119 | 1.69 | 23 | 132 | 5.90 | 7.8 | 16.1 | 95 | 127/78 ( 93) | 41/24 (30) | 10 | 4195 | 2440 | 42 |
| | | 31‡ | 104 | 1.78 | 28 | 132 | 6.07 | 7.4 | 15.8 | 97 | 140/82 (102) | 45/23 (33) | 11 | | | |
| | | 64 | 94 | 2.26 (+34%) | 40 | 133 | 6.34 | 5.9 | 15.3 | 96 | 142/80 (100) | 45/22 (31) | 4 | | | |
| 1.54 | | 11§ | 78 | 1.63 | 32 | 123 | 5.38 | 7.5 | 18.1 | 94 | 135/77 ( 96) | 23/12 (16) | 0 | 3600 | 1820 | 49 |
| #794, 76M, 1.62 | ASHD, EH, CS, old myo. infaret, AF, rt. hydrothorax | Control | 84 | 1.71 | 33 | 102 | 4.15 | 6.0 | 16.0 | 93 | 139/87 (118) | 33/16 (22) | 5 | 3256 | 2003 | 38 |
| | | 22** | 77 | 1.91 (+12%) | 40 | 118 | 4.52 | 6.2 | 15.4 | 92 | 160/100 (124) | 28/13 (20) | 3 | | | |
| | | 44 | 76 | 2.11 (+23%) | 45 | 124 | 4.71 | 5.9 | 15.1 | 93 | 168/99 (123) | 30/13 (21) | 1 | | | |
| 1.59 | | 49§ | 61 | 2.00 | 52 | 100 | 4.11 | 5.0 | 14.7 | 97 | 147/80 (101) | 30/9 (16) | 1 | 3015 | 1910 | 37 |
| #940, 51M, 2.09 | ASHD, EH, CS, MF, AF, bilat. hydrothorax | Control | 146 | 1.21 | 17 | 119 | 5.23 | 9.6 | 18.1 | 92 | 102/87 ( 91) | 28/22 (24) | — | 4040 | 2160 | 47 |
| | | 18† | 134 | 1.67 (+35%) | 26 | 125 | 5.09 | 7.5 | 17.4 | 89 | 130/96 (110) | 35/22 (28) | — | | | |
| | | 32 | 122 | 1.89 (+52%) | 32 | 121 | 4.92 | 6.4 | 17.3 | 92 | 134/96 (111) | 34/18 (25) | — | | | |

*Minutes after 1.5 mg. Digoxin via catheter.
†Minutes after 1.25 mg. Digoxin via catheter.
‡Minutes after 1.0 mg. Digoxin via catheter.
§Days after acute Digoxin study.
**Minutes after 0.75 mg. Digoxin via catheter.
For key to abbreviations see Table 1.

**Table 3**

*Hemodynamic Data in Two Patients with Pneumonia and Combined Left and Right Ventricular Failure before and after Administration of Digoxin*

| Case, age sex, BSA | Diagnosis | Time | Ventricular rate (beats/min.) | Cardiac index (L./min./M.² BSA) | Stroke volume (ml.) | Oxygen uptake (ml./min./M.² BSA) | R. Q. | A-V oxygen diff. (vol. %) | Arterial blood: Oxygen cont. (vol. %) | Arterial blood: Oxygen sat. (%) | Pressures in mm. Hg: Systemic artery s/d (mean) | Pressures in mm. Hg: Pulmonary artery s/d (mean) | Pressures in mm. Hg: Right ventricle d | TBV (ml./M.² BSA) | PV (ml./M.² BSA) | Hematocrit (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | 106 | 4.50 | 74 | 184 | 0.73 | 4.1 | 15.2 | 90 | 125/69 ( 96) | 44/16 (31) | 4 | 3250 | 1925 | 41 |
| #492, 63M, 1.74 | ASHD, EH, NST, gallop, rt. hydro- | 5* | 104 | — | — | — | — | — | — | — | 140/78 (100) | 48/16 (33) | 2 | | | |
| | pneumothorax, | 8 | 100 | 4.17 | 73 | 196 | 0.71 | 4.7 | 15.0 | 90 | | | | | | |
| | bronchopneumonia | 17 | 120 | — | — | — | — | — | — | — | 139/76 (100) | 21/— (—) | 0 | | | |
| | | 36 | 136 | 5.16 (+15%) | 66 | 201 | 0.74 | 3.9 | 15.1 | 91 | 135/76 ( 99) | 25/10 (18) | 0 | | | |
| #569, 57M, 1.84 | HCVD, EH, NST, APC, VPS, pulsus alternans, bilat. hydrothorax, bronchopneumonia | Control | 115 | 2.03 | 33 | 176 | 0.79 | 8.7 | 18.0 | 86 | 208/125 (157) | 76/44 (60) | 15 | 4150 | 1860 | 55 |
| | | 5* | 107 | — | — | — | — | — | — | — | 220/133 (161) | 77/39 (55) | 15 | | | |
| | | 13 | 107 | — | — | — | — | — | — | — | 223/128 (169) | 79/37 (53) | 12 | | | |
| | | 17 | 112 | 2.25 (+11%) | 37 | 164 | 0.79 | 7.3 | 18.4 | 86 | 196/114 (143) | 68/34 (48) | 10 | | | |
| | | 37† | 100 | — | — | — | — | — | — | — | 216/117 (151) | 59/24 (38) | 7 | | | |
| | | 46 | 150 | 2.62 (+29%) | 32 | 164 | 0.79 | 6.3 | 18.1 | 87 | 200/118 (147) | 47/29 (36) | 7 | | | |

*Minutes after 1.5 mg. Digoxin via catheter.

†Onset of atrial flutter occurred at 34 minutes.

For key to abbreviations see Table 1.

tricular rate decreased before there was any rise in cardiac output (nos. 453, 588, and 682, table 2), and in still others the ventricular rate fell at first and then became relatively stable although the cardiac output continued to rise (no. 519, table 1; nos. 806, 588, 437, and 794, table 2). Furthermore, the change in ventricular rate, both in terms of magnitude and timing, gave no indication of alterations in lesser circulation pressure.

The same dichotomy between heart rate and the other hemodynamic effects of the drug can be shown in 2 other subjects (table 3) who had a rise in ventricular rate but nevertheless had increases in cardiac output and decreases in lesser circuit pressures, the latter 2 alterations speaking for a continued myocardial effect of Digoxin. Both subjects had pneumonia (no. 492 ran a temperature of 100.2° p.r. during study) which was probably responsible for the elevated oxygen uptake. Nevertheless the respiratory quotients remained normal and stable during the observation period. In one (no. 492) sinus tachycardia increased at the seventeenth minute, and in the other atrial flutter with 2:1 and 3:1 AV response began at the thirty-fourth minute after Digoxin. Despite the more rapid ventricular rate the cardiac output rose and lesser circuit pressures continued to decline.

Further evidence of improved ventricular function following Digoxin can be found in the uniform decrease in right ventricular end-diastolic pressure; presumably the increase in systolic ejection resulting in a decrease in diastolic right ventricular volume. Better emptying of the left ventricle can be inferred from the drop in the pulmonary artery diastolic pressure in the 7 patients in whom it occurred, since in the absence of vascular disease or demonstrated vasomotoricity the level of this pressure is primarily regulated by events in the left heart. In these patients the left ventricle must have ejected more blood than was offered to it by the right and therefore as a consequence of a temporary heterodynamism of the 2 ventricles, there was a reduction in pulmonary blood volume. In 5 of the 8 patients with atrial fibrillation the pulmonary arterial diastolic pressure did not fall significantly (−1 to −4 mm. Hg); nonetheless one must assume that left ventricular function was improved, since this ventricle was able to accept from the right ventricle its additional output and deliver this additional volume to the aorta. It did so, even though it could not significantly reduce its own diastolic pressure as evidenced by the lack of change in pulmonary artery diastolic pressure. Hence there was probably no change in pulmonary blood volume. The fact that the pulmonary artery diastolic pressure remained elevated and unchanged could be explained by one of these 2 mechanisms—either the left ventricular diastolic volume had not been reduced and hence the diastolic pressure remained elevated, or, there was a change in left ventricular myocardial tone, so that, despite a fall in diastolic volume, diastolic pressure remained unchanged. The lack of change in pulmonary artery diastolic pressure cannot be ascribed to pulmonary vascular disease, since a second catheterization in 3 of these 5 revealed a later drop to virtually normal levels (table 2).

A further word should be said concerning the difference in response of the pulmonary artery diastolic pressure. It could not be related to the level of total blood or plasma volumes, as these were equally large in those who did or did not have a fall in this pressure (tables 1 and 2). The dosage of Digoxin given was also similar in the 2 groups. The etiologic factor of the heart disease and age of the patient also appear not to be different. It is interesting however that 3 of the 5 patients without this pressure change had had a previous bout of cardiac failure. In all 8 patients with atrial fibrillation the clinical story suggested the onset of symptoms of right heart failure almost as soon as left, in contradistinction to patients with sinus rhythm where left-sided symptoms antedated those of right by some time. This time difference could be interpreted as indicating a more or less simul-

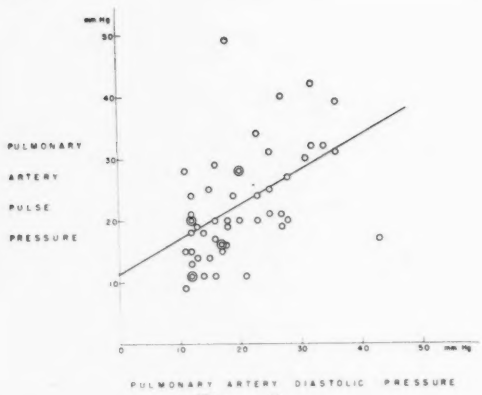


**Figure 2**

*Relationship between pulmonary artery diastolic and pulmonary artery pulse pressures when stroke volume is over 30 ml. The correlation coefficient is highly significant ($r = 0.505$, $p < 0.01$).*

taneous failure of both ventricles in atrial fibrillation, with both equally involved, while in the subject with sinus rhythm there was more involvement of the left ventricle. In the latter after Digoxin, one could say that the inotropic effect of the drug would be greater in the more involved ventricle and hence it would empty more completely. This reasoning could also apply to the first 3 patients with atrial fibrillation in table 2. In the 5 patients who did not have a fall in pulmonary artery diastolic pressure, emptying was the same for both ventricles during the acute study of Digoxin. Hence there was no immediate change in pulmonary blood volume. Later, there was a reduction in pulmonary blood volume and a fall in pulmonary artery pressures. This may have occurred either because heterodynamism appeared, with the left ventricle becoming capable of emptying more than the right, or, with a fall in total blood volume (due to diuresis) the right ventricle no longer ejected as much into the lungs, the left could still discharge this amount but could then add more of its own diastolic volume to its stroke volume and thus reduce the pulmonary blood volume.

The behavior of the pulmonary artery pulse pressure was variable. This is not surprising, since pulmonary artery pulse pressure reflects not only stroke volume but also the state of distensibility of the pulmonary vascular tree. This latter is governed by the level of pulmonary blood volume and the intrinsic characteristics of the vessels themselves. The normal pulmonary vascular bed is so distensible that relatively large changes in flow have very little effect on pressure. However once the system becomes distended, either by an increase in pulmonary blood volume or a change in the characteristics of the vasculature, then changes in volume or flow will produce changes in pressure. Thus one might expect that the greater the stroke volume or the greater the degree of pulmonary congestion, the higher will be the pulse pressure.

Since more than one physiologic variable is operating to affect pulse pressure under these conditions, their relative influence must be examined. Direct measurement of pulmonary blood volume and estimates of the characteristics of the vasculature are not yet available but one can get an indirect estimate of the degree of pulmonary congestion from the pulmonary artery diastolic pressure, provided there are no major alterations in the characteristics of the pulmonary vasculature. Since in the patients in this study one would not expect such alterations, one can assume that the diastolic pressure is largely determined by the pulmonary blood volume. Stroke volume is probably estimated fairly accurately.

Thus in order to clarify this particular problem a study of the interrelationships of pulmonary artery pulse pressure, diastolic pressure, and stroke volume was made. Since the 13 patients presented in this report would comprise a rather small group, the study was enlarged to include 67 observations in 39 patients with degenerative heart disease and pulmonary congestion. These data were secured both at rest and during exercise and include the patients found in tables 1 and 2 before digitalization. It was found that, in general, as the pulmonary artery diastolic pressure rises or falls, so does the pulmonary artery pulse pressure, as long as the stroke volume is over 30 ml. (fig. 2). The correlation coefficient is highly significant ($r = 0.505$, $p < 0.01$). Below this critical level of stroke

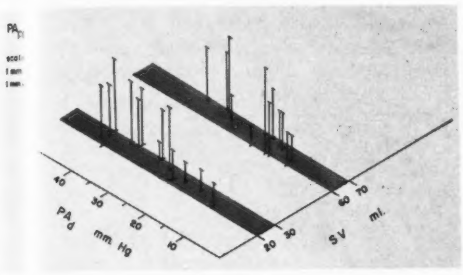


**Figure 3**

*Three-dimensional graph relating stroke volume (SV), pulmonary artery diastolic pressure ($PA_d$), and pulmonary artery pulse pressure (indicated by the vertical bars which are delimited by cross bars at their head and foot). The shaded bands enclose the 2 areas of stroke volume discussed in the text. Note that pulse pressure rises with rises in diastolic pressure when stroke volume is 60 to 70, but this is not the case when stroke volume is less than 30 ml. In the latter instance pulse pressure does not follow the rise in diastolic until the latter reaches 30 mm. Hg.*

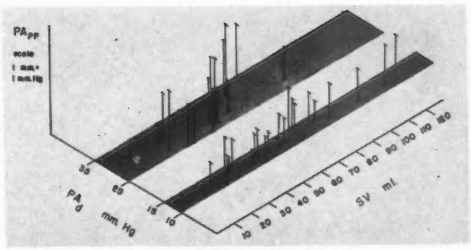


**Figure 4**

*Three-dimensional graph relating stroke volume (SV), pulmonary artery diastolic pressure ($PA_d$), and pulmonary artery pulse pressure (indicated by the vertical bars). The shaded bands enclose the 2 areas of diastolic pressure discussed in the text. Note that only when stroke volume exceeds 30 ml. does the pulse pressure rise as stroke volume grows larger, and that if the diastolic pressure is only slightly elevated (10 to 15 mm. Hg as shown in one shaded area) the stroke volume produces a smaller pulse pressure than the same stroke volume would cause at a higher level of diastolic pressure (say 25 to 35 mm. Hg as seen in the other shaded area).*

volume, there is no such correlation and pulse pressure may remain quite small, regardless of the level of diastolic pressure, unless the latter is over 30 mm. Hg (fig. 3). The influence of stroke volume on pulse pressure is not so simply defined because the level of pulmonary blood volume may also affect the relationship. As already stated, if the stroke volume is less than 30 ml., then pulse pressure remains low unless a very high level of diastolic pressure is present. Once stroke volume exceeds 30 ml., as it rises so does the pulse pressure (fig. 4). If the pulmonary artery diastolic is only slightly elevated (for example, between 10 and 15 mm. Hg as shown on fig. 4), the stroke volume produces a smaller rise in pulse pressure than the same stroke volume would cause at a higher level of pulmonary artery diastolic pressure. One can see then (fig. 5) that when stroke volume and diastolic pressure are both large, pulse pressure will be large, and when both are small, so will be the pulse pressure. Looked at from the point of view of the effect of one single variable, the higher the diastolic pressure, the higher the pulse pressure and the lower the stroke volume, the lower the pulse pressure.

The final or resultant pulse pressure in any one situation therefore will depend upon the delicate balance of the effects of these 2 variables and in all probability on which one is the more abnormal.

The variations in pulmonary artery pulse pressure seen after Digoxin can now be elucidated by considering which of the above variables is predominating as the circulation readjusts to the inotropic effect of the drug. All of the patients with sinus rhythm had a large pulse pressure (table 4) before Digoxin. In 2 (nos. 519 and 625), despite their being at the critical level of stroke volume, 29 and 30 ml. respectively, there was a very high pulmonary artery diastolic pressure and hence the latter was the dominant variable and pulse pressure was large. In the other 2 subjects stroke volume was well above the critical level, being 48 and 60 ml., hence with elevated diastolic pressures, increased pulse pressure is expected and was found. As can be seen in table 4, there was a large fall in pulmonary diastolic pressure in the first 3 subjects with sinus rhythm after the medication. Hence despite a large rise in stroke volume pulmonary artery pulse pressure fell and one can as-

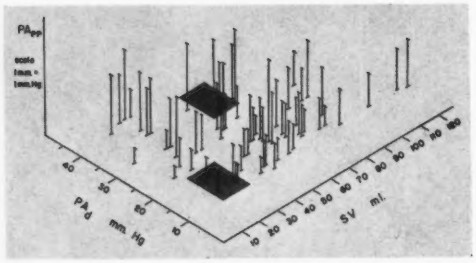


**Figure 5**

*Three-dimensional graph relating stroke volume (SV), pulmonary artery diastolic pressure ($PA_d$) and pulmonary artery pulse pressure (indicated by the vertical bars). The upper shaded rectangle marks an area where both stroke volume and diastolic pressure are large and in which pulse pressure is also large, while the lower rectangle encloses an area in which all 3 variables are small.*

sume pulmonary blood volume decreased. The fourth patient (no. 625) who had a much smaller fall in diastolic pressure with the result that this pressure did not decrease below 30 mm. Hg, responded to a rise in stroke volume (which then moved him above the critical level of 30 ml.) with a rise in pulse pressure. Since pulmonary pressures later fell markedly, (see table 1, no. 625, second study) the increased pulse pressure after Digoxin cannot be ascribed to pulmonary vascular disease but was related to a large pulmonary blood volume that later became translocated.

The 8 patients with atrial fibrillation had much smaller pulmonary artery pulse pressures before the drug than did those with sinus rhythm. The small pulse pressures were probably primarily related to the small stroke volume which was considerably less than 30 ml. in all but 1 individual (no. 794, table 4) and in this one exception it was 33 ml. Before the glycoside, the low stroke volume, by virtue of its inability greatly to distend the pulmonary tree, obscured the evidence of pulmonary congestion that might have appeared as a large pulse pressure. When Digoxin produced a very large increase in stroke volume (over 74 per cent, in table 4), distention of the tree became more evident as a rise in pulse pressure and this occurred whether or not there was a fall in pulmonary artery diastolic pressure. Therefore one can say that it occurred when pulmonary blood volume had not changed or had decreased only slightly. When stroke volume did not increase strikingly, less than 50 per cent (nos. 453, and 794 in table 4) there was little or no effect on pulse pressure. In one individual (no. 453) the 48 per cent rise in stroke volume was counterbalanced by a fall of 10 mm. Hg in pulmonary artery diastolic pressure. The other patient (no. 794) did not have much distention of the pulmonary vascular bed (as indicated by the relatively low level of diastolic pressure, 16 mm. Hg). Under such circumstances, since stroke volume was already above the critical level to begin with and rose only modestly (35 per cent) and diastolic pressure did not fall significantly, one would not expect a change in the pulse pressure.

**Table 4**

*Actual and Percentage Changes in Pulmonary Artery Diastolic, Pulse Pressure and Stroke Volume after Digoxin*

| Case no. | $PA_d$* (mm. Hg) before Digoxin | $\Delta PA_d$ (mm. Hg) | SV (ml.) before Digoxin | $\Delta$ SV (ml.) | % $\Delta$ SV | $PA_{pp}$ before Digoxin | $\Delta PA_{pp}$ (mm. Hg) | $\Delta PA_{pp}$ / $\Delta$ SV |
|---|---|---|---|---|---|---|---|---|
| **Patients with sinus rhythm** | | | | | | | | |
| 519 | 36 | −18 | 29 | +30 | +100 | 28 | − 4 | 14 |
| 616 | 25 | −19 | 48 | +28 | + 56 | 31 | −13 | 42 |
| 919 | 18 | − 6 | 60 | +11 | + 18 | 49 | −18 | 37 |
| 625 | 36 | − 6 | 30 | +10 | + 33 | 33 | +10 | + 30 |
| **Patients with atrial fibrillation** | | | | | | | | |
| 453 | 21 | −10 | 25 | +12 | + 48 | 12 | + 1 | 0 |
| 806 | 31 | − 9 | 13 | +13 | +100 | 8 | + 6 | + 75 |
| 544 | 30 | − 9 | 27 | +34 | +126 | 11 | +16 | +145 |
| 588 | 18 | − 4 | 25 | +21 | + 85 | 12 | + 5 | + 42 |
| 437 | 13 | − 1 | 22 | +33 | +150 | 13 | + 5 | + 38 |
| 682 | 24 | − 2 | 23 | +17 | + 74 | 17 | + 6 | + 85 |
| 794 | 16 | − 3 | 33 | +12 | + 36 | 17 | 0 | 0 |
| 940 | 22 | − 4 | 17 | +15 | + 88 | 6 | +10 | +167 |

*$PA_d$, pulmonary artery diastolic pressure; SV, stroke volume; $PA_{pp}$, pulmonary artery pulse pressure.

### Clinical Considerations

Several clinical implications that bear upon evaluation of the effects of such a drug at the bedside can be derived from this study. First, the amount of Digoxin given intravenously to a patient in congestive failure need not be the

so-called "digitalizing" or "full" dose (1.5 mg) in order to elicit marked hemodynamic changes toward normal. Ten of the 13 subjects received less than this dose (0.75 to 1.25 mg), and 2 of these had reached normal lesser circulation pressures at the end of the period of observation (nos. 616 and 417). The earliest moment at which any effect of the drug was noted (change in heart rate, pressures or output), was 5 minutes after the completion of the injection of drug (the administration of the drug itself took 5 minutes). All patients had had some effect from the medication by 30 minutes. It is interesting that the 2 cardiotonic effects of the drug that were measured in this study (a rise in cardiac output and a fall in lesser circulation diastolic pressures) did not necessarily occur simultaneously, i.e., one could appear before the other (nos. 919, 417, and 453). In one subject (no. 919) the right ventricular diastolic pressure fell somewhat before the pulmonary artery pressures declined and this effect was patent 10 minutes after Digoxin, before any obvious rise occurred in cardiac output. Furthermore, stroke volume had increased only slightly (5 ml.) and heart rate fallen only 6 beats. Thus it appears that improvement in ventricular function evoked by Digoxin is a complex and interdigitating series of mechanisms and the fundamental and earliest event is still unknown and is not uniformly expressed in any one hemodynamic alteration.

These observations render somewhat tenuous the present clinical method of judging digitalization in which the cardiotonic effect of the drug is timed and assumed to occur almost solely in relation to the response of the ventricular rate;[18] the implication being that if rate is not affected the myocardial effect has not occurred. This reasoning would be particularly erroneous in patients with sinus rhythm. This concept of the secondary position held by change in rate has recently been rephasized by McMichael[19] on the basis of studies made in his laboratory.[20] Although changes in rate may eventually appear following this drug, it is now clear that the contractile myocardial effects may precede them by some time. Thus one should beware of increasing the amount of glycoside early in its administration if the rate response is negligible.

Another clinical sign that has been much used to determine the so-called digitalis effect is alteration of S-T and T waves and Q-T interval of the electrocardiogram. These variables were examined in relation to the myocardial effect of the drug in 12 of the 13 patients: the one (no. 625) with left bundle-branch block was excluded. In 11 the standard leads were followed and in the twelfth only lead $V_1$ was monitored after the drug. There were no S-T shifts in any patient; in 11 of 12 there were no significant alterations in the T waves but in one subject (no. 417) $T_2$ became upright from an isoelectric contour. The Q-T interval was not always measurable due to low voltage T waves but in 7 of 9 subjects where this was feasible, there was no change and in 2 the interval shortened. It is obvious therefore that electrocardiographic signs are not constantly indicative of the hemodynamic results of this drug and that the well known S-T, T, and Q-T changes may not appear early in the period after Digoxin.

The bedside diagnosis of congestive (right and left) heart failure usually depends upon certain objective signs in addition to the symptoms of dyspnea, orthopnea, and fatigue. A mid or protodiastolic gallop, pulsus alternans, cardiomegaly, hyperventilation, pulmonary rales, hepatomegaly, peripheral venous congestion, edema, and cyanosis are also searched for. Following the hemodynamic evidences of marked improvement in cardiac function, the patients were reexamined at the end of the study period and before returning to their ward, in order to correlate the speed with which these objective signs would mirror the improved circulatory status. The gallop rhythm, when present, almost always subsided by the end of the study; pulsus alternans would often disappear, occasionally from one circulation, say the lesser, before the other, as previously reported.[21] The other signs for the most part remained unaltered at the completion of the observation period. Hence it

is apparent that rales, hepatomegaly, and edema are slower to disappear than the pressure abnormalities that may be related to their production. The lungs, liver, and subcutaneous tissues are therefore depots that may remain as passive pools of congestion and give up this state rather slowly. This fact may explain some of the clinical paradoxes one sees, e.g., where the peripheral venous pressure may be normal or the patient free of dyspnea and yet hepatomegaly, edema and rales are found. The sequence of old and recent events must be considered in such eventualities and the assumption made of previous ventricular failure and slow resolution of the congestive phenomena. On the other hand, following Digoxin there was always an early subjective improvement in dyspnea and orthopnea although hyperventilation persisted, an observation also made by Eichna et al.[9] Therefore the persistence of hyperventilation at an unchanged level does not represent a barrier to the relief of some of the dyspnea. Furthermore, the hyperventilation did not diminish in those patients with a decrease in pulmonary artery pressures even if these reached normal levels, tending to show that this ventilatory response is not closely linked with pressure elevations in the lung vessels. It is also worth noting here that there is no elevation in basal metabolic rate in these patients with congestive failure and pulmonary congestion.

The slow disappearance of some of the objective evidences of congestive failure despite indications of the cardiotonic effects of the glycoside and resolution of much if not all of the pressure abnormalities, has considerable bearing upon the clinical problem of intravenous administration of this medication in an emergency situation. It has been the practice of some to "redigitalize" a patient orally the morning or day after an intravenous dose has been given, particularly if some of the abovementioned signs are unaltered. From the observations just cited it can be seen that this oral exhibition would then in many instances be directed at a circulation and a myocardium radically different from what they had been before the intravenous dose. There is no information to suggest that in 12 to 24 hours the circulation has returned to the state in which it was found prior to the first administration and that a second large or "digitalizing" dose is needed.

### Summary and Conclusions

The acute effects of intravenous Digoxin were studied, with use of the cardiac catheterization technic, in 13 patients with hypertensive or arteriosclerotic heart disease in combined (left and right) ventricular failure. Two patients who in addition had bronchopneumonia were also included to demonstrate the dichotomy between the inotropic effects of the drug and changes in heart rate.

Digoxin produced a rise in cardiac output and a fall in right ventricular end-diastolic pressure in every case.

The readjustments of the pulmonary arterial pressures after the drug were analyzed and it became apparent that the interrelationship between stroke volume and the degree of pulmonary congestion was the basic variable regulating the several different responses found after Digoxin.

Several clinical and hemodynamic considerations bearing upon the whole concept of a "digitalizing" dosage, the relationship between hemodynamic and electrocardiographic alterations of the drug, the inadvisability of using the effect upon ventricular rate as a reliable guide to its cardiotonic behavior, and the disappearance time of the clinical signs of congestive heart failure in relation to the early hemodynamic improvements were all discussed.

### Summario in Interlingua

Le effectos acute del administration intravenose de Digoxina esseva studiate per medio del technic de catheterismo cardiac in 13 patientes con morbo cardiac hypertensive o arteriosclerotic in disfallimento ventricular combinate (sinistre e dextere). Duo patientes, qui habeva broncho-pneumonia additional, esseva etiam studiate pro demonstrar le dichotomia inter le effectos inotropic del droga e alterationes in le frequentia del corde.

Digoxina produceva un augmento del rendimento

cardiac e un reduction del tension termino-diastolic dextro-ventricular in omne le casos.

Le re-adjustamento del tension pulmono-arterial post le droga esseva analysate, e il deveniva apparente que le relation inter le volumine per pulso e le gradio del congestion pulmonar esseva le variabile fundamental que regulava le plure differente responsas observate post le uso de Digoxina.

Es etiam discutite plure punctos clinic e hemodynamic de interesse ab le puncto de vista del concepto general do un dosage "digitalisante," le relation inter le alterationes hemodynamic e electrocardiographic producite per le droga, le riscos inherente in le uso del effecto del droga super le frequentia ventricular como criterio de su action cardiotonic, e le tempore del disparition del signos clinic de congestive disfallimento cardiacin relation con le precoce melioration hemodynamic.

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# Right and Left Heart Catheterization and Angiocardiographic Findings in Idiopathic Cardiac Hypertrophy with Endocardial Fibroelastosis

*By* JOSHUA LYNFIELD, M.D., BENJAMIN M. GASUL, M.D., LAWRENCE L. LUAN, M.D., AND ROBERT F. DILLON, M.D.†

THERE has been considerable discussion in recent years about the role of fibroelastosis in the production of cardiac hypertrophy and heart failure.[1-5] It has been postulated[3] that endocardial fibroelastosis almost invariably causes cardiac hypertrophy in the adjacent ventricular musculature, probably due to the increased work necessary to contract and expand the thick fibroelastic tissue of the endocardium. It has been presumed that the thickened endocardium interferes with and limits ventricular movement from the inside in much the same way as the scar tissue deposited around the heart in constrictive pericarditis does this from the outside.[4] Thus this condition is sometimes referred to as constrictive endocardial sclerosis. This view has recently been challenged in a very thoughtful paper by Black-Shaffer.[5] His explanation of this condition is in accord with the older German literature,[6] and the views of Lev[7] and Szanto[8] that the cardiomegaly is idiopathic and primary and that the endocardial lesion is secondary. Black-Shaffer believes that fibroelastosis is a response to abnormally great tensions in the endocardium resulting especially from cardiac dilatation. He has also stressed the secondary nature of fibroelastosis occurring in cases of anomalous origin of the left coronary artery from the pulmonary artery and in obstructive lesions such as severe aortic stenosis or atresia.

The pathologic findings of subendocardial fibroelastosis are well known. It is characterized by a diffuse thickening of the endocardium associated with cardiac hypertrophy and it most frequently involves the left ventricle and the left atrium. The right heart chambers are rarely involved. The degree of involvement of the endocardium varies greatly: it may be diffusely thickened, smooth and porcelain white, but at times there is only slight involvement. The endocardial thickening is due to the proliferation of collagen and elastic tissue which extends into the myocardium. The valves may also be thickened. Left ventricular hypertrophy is almost always present but right ventricular hypertrophy may also be noted. Edwards[9] has divided these cases, according to the appearance of the left ventricle at autopsy, into the common dilated type and the rare contracted type.

In order to further the understanding of this condition we have performed left and right heart catheterization and angiocardiography in a group of 6 patients with subendocardial fibroelastosis. The results have been correlated with the clinical and autopsy findings.

## Materials and Methods

During the past 12 years we have studied 32 patients with endocardial fibroelastosis. Thirty of these patients have come to autopsy.* The majority first entered the hospital in a terminal state, precluding the possibility of hemodynamic studies. In 6 patients however, right heart catheterization was performed and 4 of these also had left heart catheterization. In 4 patients right heart catheterization was repeated after an interval of 1 to 4 years. The

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ge of the patients undergoing cardiac catheterization ranged from 6 months to 10 years. There were 4 boys and 2 girls. The diagnosis has been confirmed by autopsy in 4 patients.

Right heart catheterization was performed under light Pentothal anesthesia. At least 2 blood samples were obtained from the pulmonary artery, the right ventricle, the right atrium, and 1 sample from each of the cavae. Peripheral arterial blood samples and pressures were obtained from the femoral artery. All pressure measurements were made and recorded by means of a Sanborn electromanometer and a direct-writing apparatus. Mean pressures were obtained by electric integration. The zero point for pressure measurement was taken from the midthoracic plane. The oxygen content and capacity of the blood samples were determined by the method of Van Slyke and Neill.[10] An assumed normal oxygen consumption was used in the calculation of the cardiac output. The cardiac output was obtained by use of the Fick[11] principle, and the pulmonary resistance was calculated by application of well-known formulas.[12]

In order to compare blood flows and resistances the results have been expressed in relationship to the body surface area. Left heart catheterization was performed by Fisher's[13] modification of the Bjork[14] technic. Peripheral venous angiocardiograms were performed on all patients, and films were taken in 1 plane at 2 per second with a Fairchild unit. In 4 patients angiocardiograms were repeated after an interval of 1 to 4 years. In 1 patient the second angiocardiogram was performed with the Elema biplane unit and films were taken at a rate of 4 per second.

## Case Reports

### Case 1

A full-term white male infant, the result of an uneventful pregnancy, appeared to be developing normally until 3 months of age, when rapid respirations were noted. Physical examination on admission at 5½ months of age revealed moderate dyspnea and slight cyanosis. The rectal temperature was 103 F., the pulse was 160 per minute, and respirations were 64 per minute. The pharynx was markedly injected. The blood pressure over the right arm was 95/75 and over the left leg 110/84 mm. Hg. The neck veins were markedly distended. The heart was enlarged with the apex in the fifth left intercostal space in the anterior axillary line. The second heart sound over the pulmonary area was very loud and there was a grade-II systolic murmur over the second, third, and fourth left intercostal spaces. Rales were audible at both lung bases and the liver was palpable 4 cm. below the right costal margin. Roentgen rays of the chest revealed marked generalized cardiac enlargement and posterior displacement of the esophagus in the region of the left atrium. The electrocardiogram was interpreted as showing combined atrial enlargement and right ventricular hypertrophy.

There was slow but gradual improvement following digitalization, oxygen administration, and antibiotic therapy. Cardiac catheterization and angiocardiography were performed at 6½ months of age (table 1). He was discharged at the age of 10 months on a maintenance dose of digitalis. Subsequent electrocardiograms revealed increasing right ventricular hypertrophy and because of the possibility of a congenital mitral stenosis or cor triatriatum he was readmitted to the hospital at the age of 14 months for surgical exploration.* The patient suddenly died during the induction of anesthesia. Autopsy revealed marked hypertrophy of the left ventricle, but no dilatation. The endocardium in the region of the left ventricular outflow tract was markedly thickened. The mitral valve was thickened and the orifice measured 5.5 cm. in circumference. The right ventricle was moderately thickened and markedly dilated.

### Case 2

A Negro boy, was born by cesarean section of a hypertensive mother, after 8 months' gestation. At 7 months of age he was admitted to the hospital because of bronchopneumonia and heart failure. Physical examination revealed acute dyspnea, a rectal temperature of 101 F., respirations of 110 per minute, pulse of 140 per minute, and questionable cyanosis. The femoral pulsations were normal. A precordial bulge was present and cardiac dullness extended to the anterior axillary line. Gallop rhythm was noted, but no murmurs were heard. Rales were present at both lung bases and the liver was felt 3 cm. below the right costal margin. Roentgenograms of the chest revealed marked generalized cardiac enlargement, considerable posterior displacement of the barium-filled esophagus in the region of the left atrium, and a suggestion of left ventricular enlargement. The electrocardiogram showed combined but dominant left ventricular hypertrophy and probable left atrial enlargement.

Improvement occurred with digitalis, oxygen, and antibiotic therapy but cardiac enlargement persisted. At 10½ months of age cardiac catheterization and angiocardiography were performed (table 1). Six weeks later the infant again developed bronchopneumonia and died. The autopsy revealed marked dilatation and hypertrophy of

*Surgery was performed by Dr. E. H. Fell, Attending Cardiovascular Surgeon at Cook County Hospital.

**Table 1**

*Right Heart Catheterization Data in Six Patients with Idiopathic Cardiac Hypertrophy and Subendocardial Fibroelastosis*

| Case | Age | Sex | RA | Pressure, mm. Hg RV | PA | PC | FA | Pulmonary Resistance Index dynes sec. cm.$^{-5}$ Total | Arteriolar | $0_2$ Sat.% | C. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 6 mos. | M | 3 | 96/2 | 96/44 | 26 | | 2400 | 1290 | 96 | 1. |
| 2 | 10 mos. | M | 4 | 49/6 | 50/28 | | | 920 | | 96 | 3. |
| 3* | 18 mos. | M | 6 | 49/2 | 50/23 | 17 | | 690 | 364 | 94 | 4. |
| 3† | 2½ yrs. | M | 3 | 54/3 | 54/22 | 17 | 129/74 | 678 | 367 | 88 | 4. |
| 4* | 21 mos. | F | 5 | 59/4 | | | 93/57 | | | 95 | 3. |
| 4† | 6 yrs. | F | 5 | 89/6 | 89/48 | 19 | 95/65 | 2500 | 1770 | 94 | 2. |
| 5* | 6½ yrs. | M | 1 | 56/4 | 56/26 | 21 | | 1195 | 552 | 98 | 2. |
| 5† | 10 yrs. | M | 5 | 52/5 | 52/24 | 20 | 104/68 | 1250 | 574 | 99 | 2. |
| 6* | 7 yrs. | F | 5 | 55/5 | 55/25 | 19 | | 740 | 370 | 99 | 4. |
| 6† | 9 yrs. | F | 9 | 78/8 | — | — | 112/78 | — | — | — | — |

RA, right atrium mean pressure; RV, right ventricle; PA, pulmonary artery; FA, femoral artery; PC, pulmonary capillary or wedge; $0_2$ Sat.%, peripheral arterial oxygen saturation; CI, cardiac index.

*First catheterization.

†Second catheterization.

Diagnosis confirmed by autopsy in cases nos. 1, 2, 3, and 4.

the left ventricle. The lining of the left ventricular cavity was markedly thickened and white, resembling the icing of a cake. The left atrium was also thickened. The circumference of the mitral orifice measured 5.2 cm. Some hypertrophy of the right ventricle was also present.

**Case 3**

A Negro boy was delivered normally although his mother had gained 40 pounds during pregnancy. Apparently normal development took place up to the age of 6 months, when repeated attacks of upper respiratory infections and heart failure occurred. These attacks required numerous hospitalizations. On physical examination on the first admission respirations were 84 and the pulse was 158 per minute. There was no cyanosis or clubbing, the neck veins were not distended, and femoral pulsations were strong. The blood pressure was 98/78 in the right arm and 110/80 mm. Hg in the left leg. The cardiac apex was palpable in the fifth left intercostal space, almost to the anterior axillary line. Gallop rhythm was audible at the apex. The second sound over the pulmonary area was accentuated. A grade-II to III systolic murmur was audible at the apex. There were rales at the lung bases. The liver was palpable 3 cm. below the right costal margin. Roentgenograms of the chest revealed a marked increase in the transverse diameter of the heart, and left atrial and left ventricular enlargement. The electrocardiogram was interpreted as showing left atrial enlargement and marked left ventricular hypertrophy (fig. 1). After the infant was treated with digitalis, oxygen, and antibiotics, he made good progress and was discharged. Frequent readmissions were necessitated by upper respiratory infections and heart failure.

A year after the first admission right heart catheterization was performed. Combined right and left heart catheterization was performed at 2½ years of age. The physical findings at subsequent admissions were much the same as at first, except for the development of a precordial bulge, further lateral displacement of the cardiac apex, and the development of pitting edema of the lower extremities during attacks of heart failure. At the age of 4 years the patient died during an attack of bronchopneumonia associated with severe heart failure. At autopsy the left ventricle revealed marked dilatation, moderate hypertrophy, and a diffuse cloudy white thickening of the endocardium which was maximal in the outflow tract. The left atrium was dilated and the endocardium was moderately thickened. The circumference of the mitral orifice was 9.4 cm. exceeding that of the tricuspid orifice which measured 8.5 cm. The mitral valve leaflets were thin and supple. The right heart chambers were also hypertrophied and dilated.

**Case 4**

A Negro girl was admitted to the hospital for heart failure at the age of 18 months. Physical examination revealed an underdeveloped lethargic

boy with slight cyanosis. The rectal temperature was 99 F., the pulse was 140 per minute, and the respirations were 40. Femoral pulsations were normal. The heart was markedly enlarged with the cardiac apex in the fifth left intercostal space at the anterior axillary line. Gallop rhythm was present. The liver was palpable 4 cm. below the right costal margin. She responded slowly to digitalization and was studied by cardiac catheterization and angiocardiography 3 months after admission. Four weeks later she was discharged on maintenance digitalis therapy.

She was subject to frequent colds accompanied by weakness and dyspnea. Heart failure recurred at the age of 3 and 6 years. Pertinent physical findings at the age of 6 years revealed a poorly developed girl with marked dyspnea, respirations at 60 per minute, generalized edema, and a pulse of 128 per minute. Blood pressure was 105/80 over the right arm, and the femoral pulses were normal. The heart was markedly enlarged and a diffuse precordial bulge was present. The second heart sound over the pulmonary area was markedly accentuated and a loud third heart sound was present. No murmurs were heard. There was evidence of a small right pleural effusion, and crepitant rales were present throughout both lungs. Ascites was also present and the liver was enlarged 9 cm. below the right costal margin. Chest roentgenograms revealed marked generalized cardiac enlargement, with left atrial and probable right ventricular enlargement. The electrocardiogram (fig. 2) showed marked right atrial enlargement and right ventricular hypertrophy. She responded well to digitalis, Mercuhydrin, a low-salt diet, and bed rest. Cardiac catheterization and angiocardiography were again performed. In view of the demonstration of severe pulmonary hypertension it was decided to establish the absence of a correctible lesion by means of a surgical exploration. At operation the surgeon* found a markedly dilated left atrium but no evidence of obstruction at the mitral valve. He also noted that the cavity of the left ventricle was small. Ventricular fibrillation occurred suddenly during the operation and the patient died, despite all attempts at resuscitation. Autopsy revealed marked dilatation and fibroelastosis of the left atrium. The mitral valve orifice measured 6.5 cm. in circumference and the leaflets were thin and supple. The left ventricular chamber was small, its muscle wall was hypertrophied, and the endocardium at the apex was thickened. The right heart chambers were markedly dilated and hypertrophied.

*Surgery was performed by Drs. E. H. Fell and M. Weinberg.

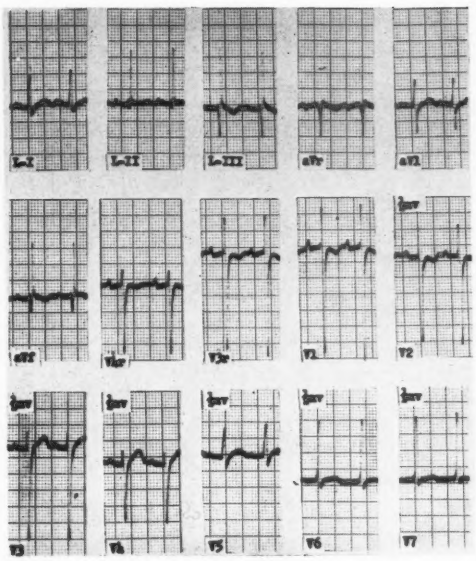


**Figure 1**

*Electrocardiogram of case 3, the dilated type I, taken at 2 years of age. Note wide bifid P wave over lead I indicative of left atrial enlargement. The deep S waves over the right precordial leads and tall R waves over left precordial leads are indicative of left ventricular hypertrophy.*

**Case 5**

A 4-year-old Negro boy suffering from easy fatigability and inability to keep up with other children, was admitted to the hospital for investigation. He was the product of a full-term spontaneous delivery. Physical examination on admission revealed a thin, underdeveloped boy in no discomfort. The blood pressure was 90/60 mm. Hg over the right arm, and the femoral pulses were normal. There was no cyanosis or clubbing. The heart was not enlarged, the cardiac apex was in the fourth left intercostal space inside the midclavicular line. The second heart sound over the pulmonary area was accentuated, an opening snap was heard, and there were no murmurs. There were no rales in the lungs and the liver was not enlarged. A chest roentgenogram showed the heart to be of normal size but there was a slight bulge over the pulmonary area. The electrocardiogram was interpreted as showing slight right ventricular hypertrophy. An angiocardiogram was performed at this time. He was discharged from the hospital after 3 weeks.

Upper respiratory infections were frequent and his disability persisted. At the age of 6 years he was readmitted for further study. Cardiac catheterization demonstrated moderate pulmonary hy-

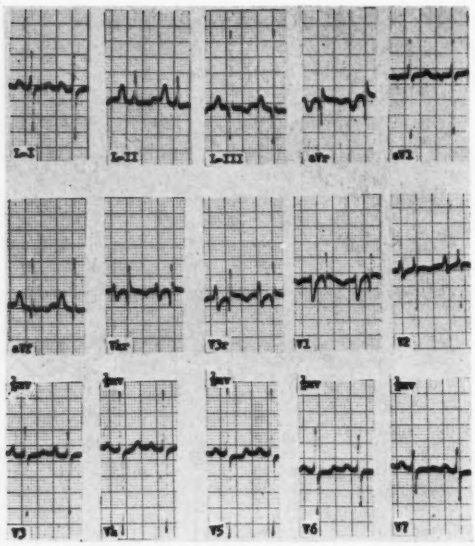

**Figure 2**

*Electrocardiogram of case 4, the contracted type II, at 6 years of age. Note very tall P wave over lead II indicative of right atrial enlargement. The tall R waves over the right precordial leads and the deep S waves over the left precordial leads indicate right ventricular hypertrophy.*

pertension and an elevated pulmonary wedge pressure. Surgical exploration was advised to rule out the presence of a correctable lesion. At surgery* a portion of the left atrial appendage was incised, the endocardium was noted to be creamy white and markedly thickened. The mitral valve was found to be normal to palpation and no stenosis was felt. The patient made an uneventful recovery.

Easy fatigability persisted, and he was readmitted at the age of 10 years for a combined right and left heart catheterization. The cardiac apex was in the fifth left intercostal space just inside the midclavicular line, there was a slight lower left parasternal lift, and the second heart sound was palpable over the second and third left intercostal spaces. The first heart sound was normal and the second heart sound was markedly accentuated over the pulmonary area. An opening snap was heard at the apex and in the fifth left intercostal space parasternally (fig. 3). There were no murmurs. A chest roentgenogram revealed slight to moderate cardiac enlargement and enlargement of the left and right atrium. The electrocardiogram showed left atrial enlargement and right ventricular hyper-

*Performed by Dr. E. H. Fell.

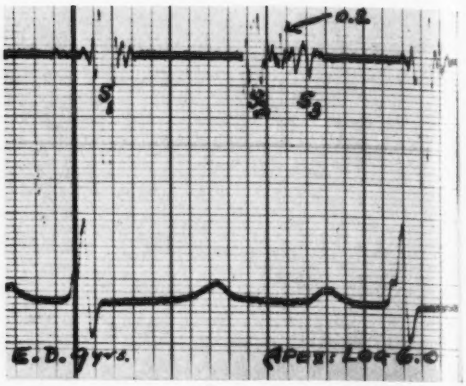


**Figure 3**

*Phonocardiogram of case 5, type II at 9 years of age. High-frequency recording from the cardiac apex. Note the opening snap of the mitral valve following the second heart sound. $S_1$, first heart sound; $S_2$, second heart sound; $S_3$, third heart sound; O.S., opening snap.*

trophy. The pulmonary arterial pressure obtained at right heart catheterization had remained almost the same as before. The patient was discharged from the hospital and is still being followed in the outpatient clinic.

**Case 6**

A 7-year-old Negro girl, was admitted to the hospital with a history of frequent colds and easy fatigability of several years' duration. She became dyspneic after running 1 block or walking 8 blocks. There was no history of rheumatic fever. She was a full-term baby, the result of a normal spontaneous delivery and weighed 6 pounds, 12 ounces at birth. Physical examination revealed a somewhat underdeveloped girl in no discomfort. There was no cyanosis or clubbing. The blood pressure was 90/60 over the right arm and 120/70 mm. Hg over the left leg. The heart was not enlarged to percussion. The second heart sound over the pulmonary area was markedly accentuated. A few coarse rhonchi were present in both lungs. The liver was not enlarged and there was no peripheral edema. Chest roentgenograms revealed evidence of left ventricular enlargement. The electrocardiogram showed left atrial enlargement and left ventricular hypertrophy and strain. Cardiac catheterization and angiocardiography were performed. She was discharged from the hospital and followed in the outpatient clinic at regular intervals.

Her disability continued and she was readmitted to the hospital at the age of 10 years for left and right heart catheterization. Physical examination

revealed no cyanosis or clubbing and no evidence of congestive heart failure. The pulse was 84 per minute and regular. The blood pressure was 110/90 over the right arm. The cardiac apex, which had a forceful left ventricular character, was located in the fifth left intercostal space just outside the midclavicular line. The first heart sound was normal and maximal at the apex. The second heart sound was loud, closely split, and maximal over the second left intercostal space with a dominant pulmonic component. A loud early systolic ejection sound was audible over the pulmonary area, and an opening snap was present at the apex. The auscultatory findings were confirmed by phonocardiography. Roentgenograms of the chest revealed slight cardiac enlargement, posterior displacement of the esophagus in the region of the left atrium, and evidence of left ventricular enlargement.

Following cardiac catheterization the patient was discharged from the hospital to the outpatient clinic. She was readmitted 6 months later in congestive heart failure, which responded to digitalis, Mercuhydrin, low-salt diet, and bed rest. After 3 weeks she was discharged again on digitalis and is being followed at regular intervals in the outpatient clinic.

### Right Heart Catheterization Data

The right heart catheterization data in 6 patients with fibroelastosis are reported in table 1. Three patients (nos. 2, 3, and 5) revealed moderate pulmonary hypertension, and the rest (nos. 1, 4, and 6) showed severe pulmonary hypertension with a systolic pressure over 75 mm. Hg. The cardiac index was decreased in 3 patients (nos. 1, 4, and 5), in 1 patient (no. 4) it was normal at the first cardiac catheterization and fell below normal 4 years later. The total pulmonary resistance index for the whole group was markedly increased and ranged from 690 to 2500 dynes sec. cm.$^{-5}$. About half the total pulmonary resistance was due to the elevated pulmonary capillary pressure and the rest was due to the pulmonary arteriolar resistance.

Four patients (nos. 3, 4, 5, and 6) were recatheterized at intervals of 1 to 4 years. In 2 patients (nos. 4 and 6) recatheterized after 4 and 2 years, the right ventricular systolic pressure rose 30 and 23 mm. Hg respectively. In case 6 the pulmonary artery wedge pressure at the first cardiac catheterization was 19 mm. Hg and 2 years later the left ventricular end diastolic pressure was 39 mm. Hg. This represented a marked rise in left ventricular diastolic pressure, because we may assume that the pulmonary artery wedge pressure reflected the left ventricular diastolic pressure. The rise in the pulmonary arterial pressure was best accounted for by the rise in the left ventricular diastolic pressure. The reason for the increase in pulmonary arterial pressure in case 4 was not definitely determined because the pulmonary artery wedge pressure could not be obtained at the first cardiac catheterization. The cardiac index had decreased in case 4 at the second catheterization. Due to technical reasons the cardiac index could not be obtained at the second catheterization in case 6, therefore no comparisons were possible. The other 2 patients (nos. 3 and 5), who were recatheterized at intervals of 1 and 3½ years respectively, revealed no significant change in the pulmonary artery and wedge pressures. The pulmonary resistance and the cardiac index in these patients also showed no significant changes.

**Table 2**

*Left Heart Catheterization Data in Four Patients with Idiopathic Cardiac Hypertrophy and Subendocardial Fibroelastosis*

| Case | Age | Sex | Pressures in mm. Hg | | | |
|---|---|---|---|---|---|---|
| | | | Left atrial mean pressure | Left ventricle | | |
| | | | | Systole | Early diastole | Late diastole |
| | | | | 113* | | |
| 3 | 2½ yrs. | M | 26 | 88 | 23 | 23 |
| 4 | 6 yrs. | F | 22 | | | |
| 5 | 10 yrs. | M | 28 | 104 | 24 | 29 |
| 6 | 9 yrs. | F | | 112 | 19 | 39 |

*Pressure recorded during ventricular bigeminy.

Case 4, left ventricle not entered. Case 6, the left atrium was not entered; the left ventricle was entered by retrograde catheterization across the aortic valve.

### Left Heart Catheterization Data

The left heart catheterization data of 4 patients (nos. 3, 4, 5, and 6) are shown in table 2. In 1 patient (no. 6) the left atrium could

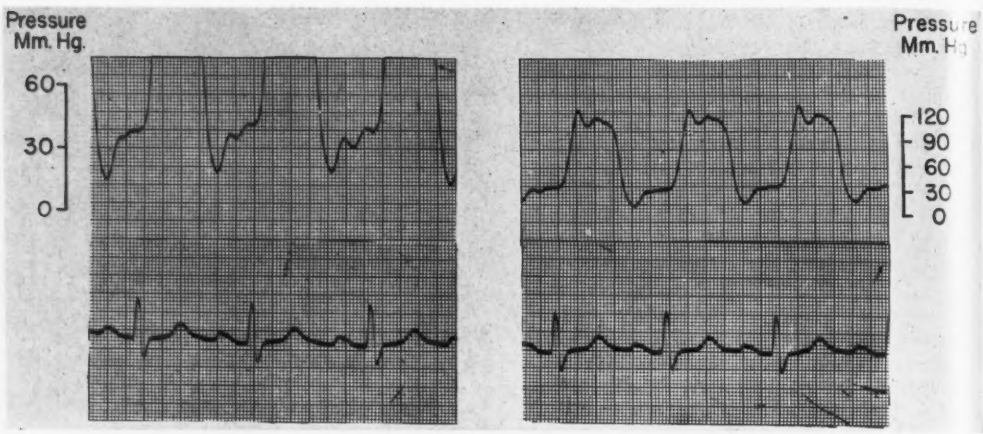


**Figure 4**

*Left ventricular pressure tracing of case 6, the dilated type I, at age of 9 years. Paper speed 50 mm. per second.* Left. *Pressure recorded on range 40.* Right. *Pressure recorded on range 100. Note the elevated left ventricular diastolic pressure and the early diastolic dip followed by a plateau.*

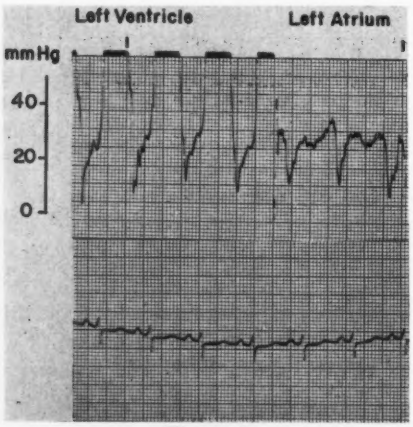


**Figure 5**

*Left atrial and left ventricular pressure recording from case 5, type II, at 10 years of age. Record obtained during withdrawal of catheter from left ventricle to left atrium. Range 40, paper speed 25 mm. per second. Note elevated left atrial and left ventricular diastolic pressure. Early diastolic dip in the ventricular tracing. M or W shape of left atrial tracing, with the major negative deflection corresponding to the early diastolic dip in the ventricular tracing and the smaller negative wave occurring during ventricular systole.*

not be entered, hence retrograde left ventricular catheterization was performed by advancing a catheter from the femoral artery across the aortic valves. In another patient (no. 4), the left ventricle could not be entered, and only left atrial pressure pulse records were obtained. The most important finding in all was a markedly elevated left ventricular diastolic pressure in excess of 20 mm. Hg, indicative of left ventricular failure. The highest in case 6 measured 39 mm. Hg in presystole.

A distinctive left ventricular diastolic pressure pulse tracing was found in 2 patients (nos. 5 and 6). In case 6 there was a marked early diastolic dip and plateau (fig. 4), such as may be seen in cases of heart failure,[15] constrictive pericarditis,[15, 16] diffuse myocardial fibrosis,[17] and amyloid infiltration of the heart muscle.[18] In case 5 the ventricular tracing revealed a steep, early diastolic dip (fig. 5) followed immediately by a sharp upstroke and a further rise of pressure due to left atrial contraction. A diastolic plateau would probably have been demonstrable at a slower heart rate. The other patient (case 3) in whom a left ventricular pressure tracing was obtained maintained a persistent bigeminy during the procedure. During the long diastolic intervals the ventricular pressure pulse assumed a flattened contour.

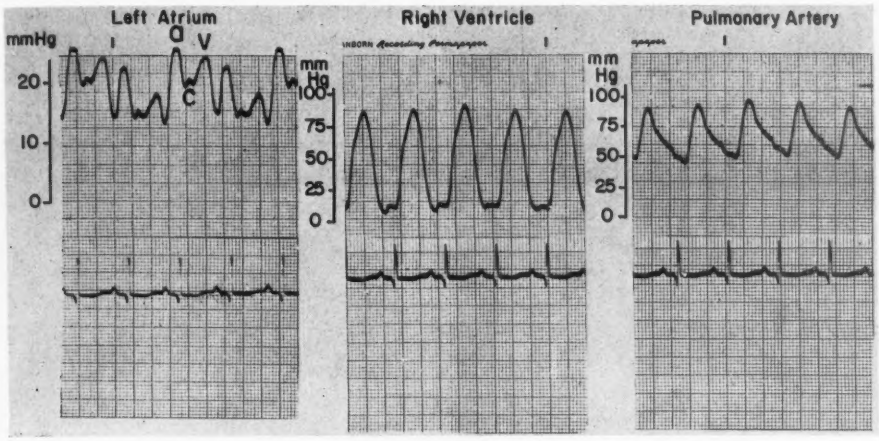


**Figure 6**

*Pressure recording from left atrium, right ventricle, and pulmonary artery. Case 4, type II, at 6 years of age. Left atrial pressure tracing on range 20 reveals an elevated left atrial pressure. The a wave is somewhat prominent. There is marked elevation of the right ventricular and pulmonary arterial pressure.*

A distinctive left atrial pressure tracing was found in 1 case (no. 5) which revealed an M- or W-shaped contour (fig. 5), such as that seen in the aforementioned conditions associated with an early diastolic dip in the ventricular tracing. The principal negative wave corresponded with the early diastolic dip of the ventricular tracing and the smaller negative wave occurred during ventricular systole. Similar findings would be anticipated in case 6, the patient with the marked early diastolic dip and plateau in the ventricular tracing, but it was not possible to enter the left atrium. The left atrial tracings of the other 2 patients were not very remarkable. In case 4, the patient with the small left ventricular cavity, the mean left atrial pressure measured 22 mm. Hg, and we assume that the left ventricular diastolic pressure was similarly elevated because no mitral stenosis was demonstrable at autopsy. The left atrial pressure tracing revealed a prominent *a* wave (fig. 6). In case 3, the patient with the markedly dilated left ventricle, the left atrial pressure tracing obtained during sinus rhythm revealed a prominent *v* wave suggestive of some mitral regurgitation.

**Angiocardiographic Findings**

Venous angiocardiograms were performed in all patients and were repeated after an interval of 1 to 4 years in 3 cases (nos. 3, 4, and 5). In 1 patient (no. 3) the second angiocardiogram was performed by advancing a catheter across the aortic valves into the left ventricle. The angiocardiograms were divided into 2 groups: those showing dilatation of the left ventricle (cases 2, 3, and 6) and those with a small or normal-sized left ventricular chamber (cases 1, 4, and 5). In all patients opacification of the left side of the heart was delayed and prolonged.[19] The left atrium appeared to be enlarged in all but 1 patient (no. 2). There was evidence of considerable contraction of the left atrium in the angiocardiograms of 2 patients (case 6 and in the first angiocardiogram of case 3). In the posteroanterior view left ventricular enlargement resulted in a concave appearance of the septal wall of the right ventricle in 2 patients (cases 2 and 3).

The patients with the most severe degree of left ventricular dilatation revealed the smallest change in left ventricular chamber size during ventricular systole. The angiocardiographic findings associated with marked

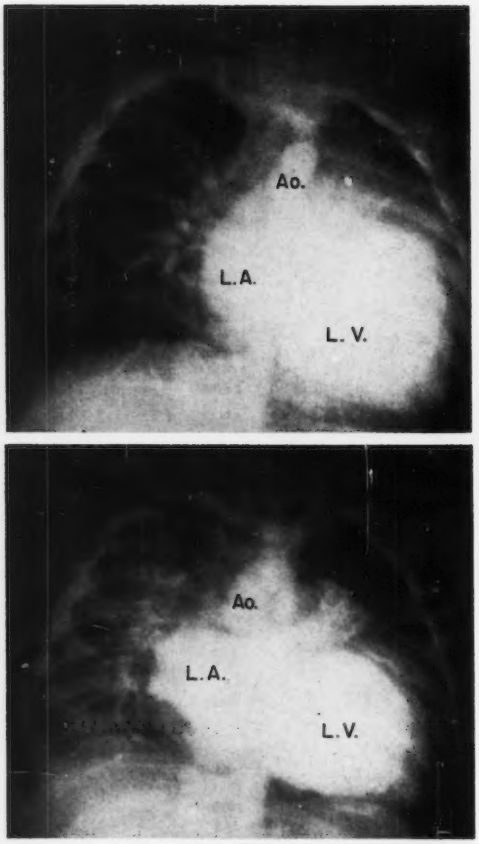


**Figure 7**

Top. *Frontal angiocardiogram at 6 seconds. Case 3, type I, at 6 months of age. Note marked left ventricular dilatation. The left ventricle is in diastole and the left atrium in systole,* bottom, *at 6½ seconds. The left atrium is in diastole and the left ventricle in systole. Note small change in left ventricular volume accompanying systole, and the large residual volume. Note also considerable volume change accompanying left atrial systole.*

left ventricular dilatation are illustrated by cases 2 and 3. In case 2 there appeared to be no appreciable change in the size of the left ventricular cavity during systole and diastole. The first angiocardiogram of case 3 at the age of 6 months revealed marked left ventricular enlargement. Decrease in chamber size during left ventricular systole was present but the residual volume was large. The left atrium was also enlarged but contracted well during

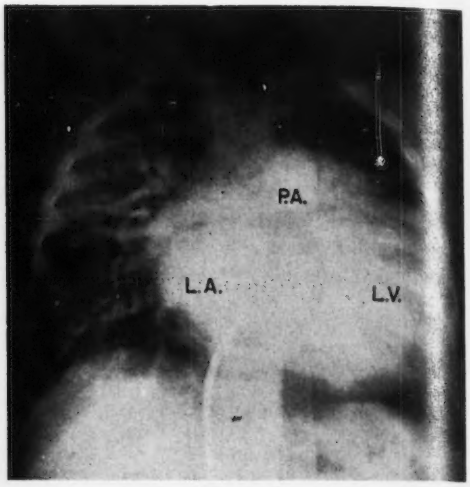


**Figure 8**

*Frontal angiocardiogram at 5½ seconds. Case 3 at 18 months of age. The left ventricle shows further dilatation as compared to 6 months of age. Left ventricular volume changes during systole and diastole were even smaller than at 6 months of age. Prolonged opacification of the pulmonary artery is also present.*

atrial systole (fig. 7). The angiocardiogram obtained a year later appeared to show further dilatation of the left heart chambers. The left ventricle revealed even less change in volume during systole and diastole than previously (fig. 8). The right heart chambers were also enlarged.

A review of the angiocardiograms of the patients with mild dilatation of the left ventricle and those with a normal or contracted left ventricular chamber (cases 1, 4, 5, and 6) revealed a considerable decrease in the volume of the left ventricle in systole. Case 6 for example, (fig. 9) revealed mild to moderate dilatation of the left ventricle and slight enlargement of the left atrium. A considerable decrease in left ventricular size occurred in systole but the residual volume was increased and opacification of the left heart chambers was prolonged. A selective angiocardiogram with the catheter in the left ventricle 2 years later showed similar findings. The angiocardiogram of case 5 at 6½ years of age revealed slight enlargement of the left atrium.

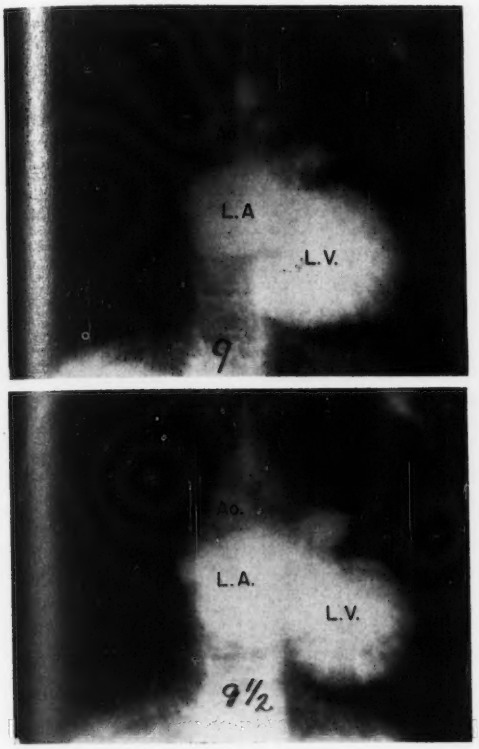


**Figure 9**

*Frontal angiocardiogram of case 6, type I, at 7 years.* Top. *At 9 seconds the left ventricle is in diastole; it is moderately enlarged. The left atrium is in systole;* bottom, *at 9½ seconds, the left ventricle in systole. Note decrease in volume and large residual volume. Left atrium in diastole. Note considerable change in left atrial volume following systole.*

The diastolic volume of the left ventricle appeared to be more or less within the limits of normal but the contour of the chamber was abnormally spherical. Despite a considerable decrease in left ventricular volume during ventricular systole the residual volume appeared to be somewhat increased and there was prolonged opacification of the left heart chambers (fig. 10).

The angiocardiogram of 2 patients (nos. 1 and 4) revealed a somewhat small left ventricular cavity. In both patients a considerable decrease in volume occurred during left ventricular systole (fig. 11), however, the residual volume in case 4 appeared to be increased. Markedly prolonged opacification of the left heart chambers was also present in both patients. The left atrium was enlarged in both but did not appear to contract well. The right ventricle in contrast to the left was enlarged, especially in case 4. The aorta in both patients appeared to be normal.

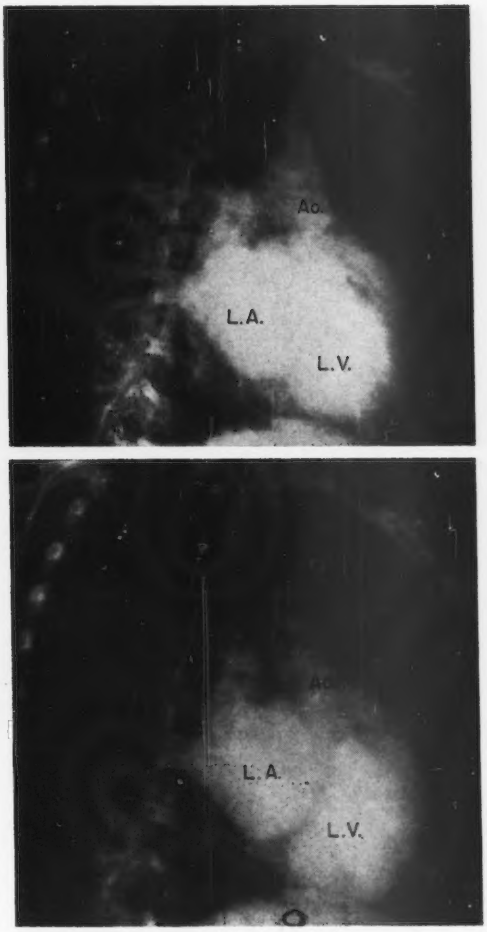


**Figure 10**

*Angiocardiogram of case 5, type II, at 6½ years of age.* Top. *Right anterior oblique view at 7½ seconds. Note enlarged left atrium. The left ventricle is in systole,* bottom, *at 8 seconds left ventricle is in diastole. Note marked change in volume in systole and diastole. The size of the left ventricular cavity appears to be within normal limits, but it is abnormally spherical.*

It is interesting to correlate the angiocardiographic findings with the left heart catheterization data. Case 6 with left ventricular dilatation showed a high left ventricular end diastolic pressure and an early diastolic dip and plateau. Case 5, on the other hand, with a normal-sized left ventricular cavity also illustrated a markedly elevated left ventricular diastolic pressure and an early diastolic dip in the left ventricular pressure pulse tracing. These findings suggest that similar pressure pulse changes may be found in patients with left ventricular failure and dilatation (case 6) as in the patients with left ventricu-

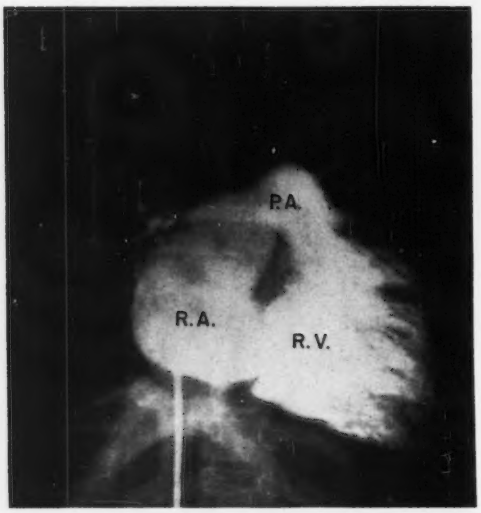


Figure 11a

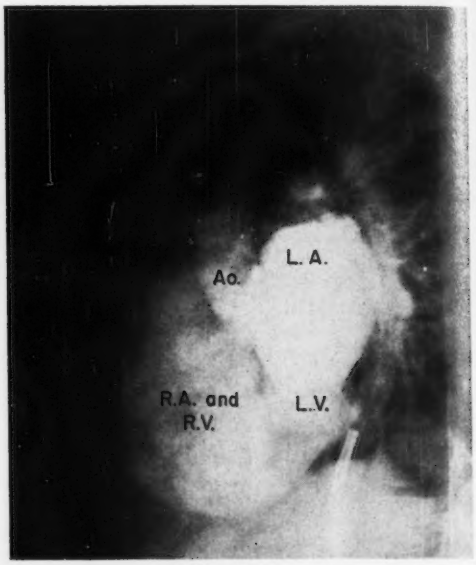


Figure 11c

Figure 11b

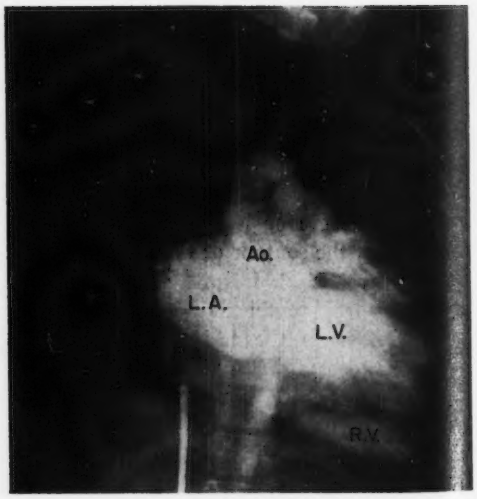


Figure 11d

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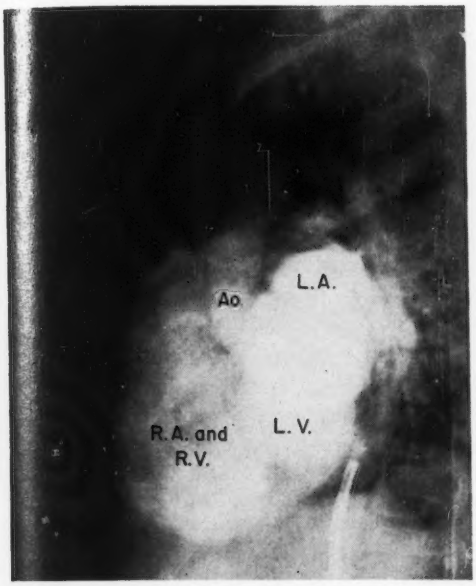


**Figure 11e**

*Angiocardiograms of case 4, type II at 6 years of age.* a, *Frontal view at 5¾ seconds, there is prolonged opacification of the right heart chambers. Note marked enlargement of the right atrium and of the right ventricle.* b, *Frontal angiocardiogram at 12¾ seconds. Left ventricle in systole. Note enlarged left atrium. The markedly enlarged right atrium and right ventricle are still slightly opacified.* c, *Lateral angiocardiogram at 12¾ seconds. Left ventricle in systole is just visible below the left atrium. Note markedly enlarged right heart chambers.* d, *Frontal angiocardiogram at 13 seconds. The left ventricle is in diastole. Note small size of left ventricular chamber in comparison with the large right ventricle. Note change in left ventricular volume in diastole, and also lack of change in the left atrial volume.* e, *Lateral angiocardiogram at 13 seconds. Note increased size of left ventricle during left ventricular diastole.*

lar failure with a normal or even contracted left ventricular cavity (case 5). Because of the similarity of the pressure pulse changes the angiocardiographic findings are most helpful in deciding which type of failure is present. The type of failure with a normal or contracted left ventricular cavity characterized mainly by impaired distensibility of the ventricle is similar to that found in patients with certain pericardial and myocardial diseases such as constrictive pericarditis[15, 16] diffuse myocardial fibrosis,[17] and amyloid infiltration of the heart muscle.[18]

**Discussion**

Our cases of fibroelastosis are divided by means of angiocardiography into 2 types: those with a dilated left ventricle and those with a normal sized or contracted left ventricular cavity. This division agrees well with Edwards' classification.[9] The clinical and electrocardiographic findings tended to reflect this subdivision into 2 types. The patients with the dilated type of left ventricular chamber reveal evidence of marked left ventricular enlargement and hypertrophy on clinical, roentgenologic, and electrocardiographic examination. Clinical and electrocardiographic evidence of associated right ventricular hypertrophy may also be present.

The patients with a normal-sized or small left ventricular chamber revealed primarily clinical evidence of pulmonary hypertension and right ventricular hypertrophy, the latter being especially marked in the electrocardiogram. Lambert's[20] views relating to the electrocardiographic changes in the contracted and dilated type of fibroelastosis are in agreement with our findings.

Two of our patients (nos. 5 and 6) presented on auscultation an opening snap of the mitral valve, which was also demonstrated by phonocardiography. One of the patients (no. 6) belonged to the type with a dilated left ventricle and the other (no. 5) to the type with a normal or contracted left ventricular cavity. Surgical exploration was advised in 1 patient (no. 5) because the opening snap raised the possibility of mitral stenosis. At surgery no evidence of mitral stenosis was found. The opening snap in our patients was undoubtedly due to some thickening of the mitral valve, which is not infrequently present in patients with endocardial fibroelastosis.

There are only a few reports in the literature describing right heart catheterization data in patients with endocardial fibroelastosis. Adams[21] reported 4 patients: the

pressures in the lesser circulation were entirely normal in 2 of them and the other 2 had only slight pulmonary hypertension. Nadas[22] studied 3 cases with mild elevation of the pulmonary arterial and pulmonary capillary pressures. Lambert[20] reported 4 patients and found moderate to marked pulmonary hypertension and elevation of the pulmonary wedge pressure in all of them. Our findings, which are in agreement with those of Lambert, suggested in addition that patients with marked left ventricular dilatation develop moderate pulmonary hypertension, whereas those with mild left ventricular dilatation and those with a normal or small left ventricular chamber tend to develop more severe pulmonary hypertension. The main cause of pulmonary hypertension is related to the elevated left ventricular diastolic pressure. The pulmonary resistance was elevated in all patients and markedly so in those with severe pulmonary hypertension.

We were able to find reference to only 1 patient who was studied by left heart catheterization. Lambert[20] found a diastolic pressure of 22 mm. Hg in the left ventricle but did not comment on the contour of the left ventricular diastolic pressure. In our group of patients left heart catheterization revealed a marked elevation of the left ventricular diastolic pressure which was regarded as indicative of left heart failure. A distinctive left ventricular diastolic pressure tracing with an early diastolic dip was present in 2 patients, one with left ventricular dilatation and the other with a normal-sized left ventricular cavity. This finding suggested that the left ventricular diastolic pressure pulse tracing was similar in cases of left ventricular failure with mainly impairment of systolic contractility and a dilated left ventricle, and in those with predominantly impaired distensibility and a normal or contracted left ventricular cavity.

Angiocardiography in the patients with marked left ventricular dilatation revealed markedly reduced volume changes during systole and diastole in the left ventricle. On the other hand the patients with mild left ventricular dilatation and those with a normal-sized or small left ventricular cavity revealed considerable volume changes in systole and diastole. But in spite of these volume changes, the residual volume in all but 1 patient (no. 1) was increased. Prolonged opacification of the left heart chambers, which appears to be due mainly to impairment of left ventricular contractility or distensibility, was present in all patients. It has been suggested[23] that greatly reduced systolic and diastolic volume changes in the left ventricle are a characteristic angiocardiographic finding of fibroelastosis and related to the splinting action of the endocardium. Our angiocardiographic findings, however, do not support this conclusion but show instead that reduced volume changes are related to the degree of left ventricular dilatation. Our findings are in agreement with the observation that a markedly dilated heart undergoes much smaller volume changes than a normal heart during the ejection of a normal stroke volume.[24] We have seen these reduced volume changes in other conditions such as in nonspecific myocarditis and in marked left ventricular failure from other causes. We believe that reduced volume changes during systole and diastole in the left ventricle are frequently seen in fibroelastosis only because this condition is so frequently associated with left ventricular dilatation. The authors who suggest this angiocardiographic finding as a characteristic of fibroelastosis described only patients with the dilated type of endocardial fibroelastosis.

We agree with Prec and Cassels[25] and Lambert[20] that the dominant defect in the cases with left ventricular dilatation appears to be impairment of systolic emptying. This results in a progressively larger residual volume and left ventricular dilatation. The sequence of progressive left ventricular dilatation was illustrated by one of our patients (no. 3) and by the case of Prec and Cassels,[25] a female infant with a normal-sized heart after birth who developed progressive cardiac enlargement at the age of 3 months and died at 8 months of age. Autopsy revealed marked fibroelastosis of the left ventricle and the left

atrium. These cases illustrating progressive left ventricular dilatation are further evidence against the view that endocardial fibroelastosis has a constrictive effect on the heart. Evidence of left ventricular failure was present in all our cases of idiopathic cardiac hypertrophy with endocardial fibroelastosis. Chronic left ventricular failure was present in two thirds of the cases. The principal difficulty in those with the dilated type of left ventricle appeared to be an impairment of systolic contractility, whereas impairment of ventricular distensibility appeared to be the main difficulty in those with the normal-sized or contracted left ventricle. Some impairment of contractility was also noted in the latter. Functionally, the cases with a normal-sized or contracted left ventricle appear to resemble cases of constrictive pericarditis[26] or of diffuse myocardial fibrosis[18] involving the left ventricle. The secondary effects on the pulmonary circulation are similar to those of mitral stenosis. The cause of the impairment of left ventricular function in the 2 types is as yet unknown.

The extent and degree of endocardial thickening involving the left ventricle was quite variable, in 2 patients it was marked, in 1 it was moderate, and in 1 it was only slight. However, moderate or marked fibroelastosis was present in the left atrium in all 4 autopsied patients, and in 1 who is still alive.

In the light of the similarity of our left heart catheterization and angiocardiographic findings irrespective of the degree of endocardial thickening, it appears that the endocardial thickening is not the primary lesion but a secondary phenomenon. We favor the view of Black-Shaffer[5, 27] that endocardial fibroelastosis develops in response to increased tension on the heart and that it supports rather than hinders myocardial function.

In order to shift the emphasis from the secondary finding of the thickened endocardium to the primary idiopathic cardiac hypertrophy we suggest, in complete agreement with Black-Shaffer[5] and Lev,[7] that the term endocardial fibroelastosis be discarded. Instead we prefer the term "idiopathic cardiac hypertrophy type I or type II with endocardial fibroelastosis." Type I is associated with left ventricular hypertrophy, dilatation and failure. Type II is associated with pulmonary hypertension and right ventricular hypertrophy secondary to disease of a normal-sized or contracted left ventricular chamber.

### Conclusions

During the past 12 years we have studied 32 patients with endocardial fibroelastosis. Six of these patients have been studied by means of clinical, roentgenologic, electrocardiographic, and phonocardiographic examinations. Right heart catheterization in combination with left heart catheterization was performed in 4, and 2 patients were studied by right heart catheterization alone. Angiocardiograms were performed in all 6. The diagnosis was confirmed by autopsy in 4 of the 6 cases.

On the basis of the clinical, roentgenologic, electrocardiographic, cardiac catheterization, and angiocardiographic findings, we divide the patients into 2 types: Type I is characterized by a dilated left ventricle and signs of left ventricular enlargement and failure. Type II is characterized by a normal-sized or contracted left ventricular cavity and more prominent findings of pulmonary hypertension and right ventricular hypertrophy secondary to impaired left ventricular function. This classification agrees well with Edwards' pathologic classification.[8] The basic lesion appears to be a disturbance of myocardial function, the cause of which has not yet been determined. In common with other authors[5, 7] we prefer the term "idiopathic cardiac hypertrophy type I or type II with endocardial fibroelastosis" to that of endocardial fibroelastosis.

### Summario in Interlingua

In le curso del passate 12 annos, nos ha studiate 32 patientes con fibroelastosis endocardial. Sex de iste patientes esseva studiate per medio de examines clinic, roentgenologic, electrocardiographic, e phonocardiographic. Catheterismo dextero-cardiac in combination con catheterismo sinistro-cardiac esseva effectuate in 4, e 2 patientes esseva studiate per catheterismo dextero-cardiac sol. Angiocardiogrammas esseva obtenite in omne le 6 casos. Le diagnose esseva confirmate necropticamente in 4.

Super le base del constatationes clinic, roentgeno-

logic, electrocardiographic, cardio-catheteric, e angiocardiographic nos divide le patientes in 2 typos. Typo I es characterisate per dilatation del ventriculo sinistre e signos de allargamento e discompensation sinistro-ventricular. Typo II es characterisate per dimen siones normal o per contraction del cavitate sinistro-ventricular e per plus prominente manifestationes de hypertension pulmonar e de hypertrophia dextero-ventricular como effecto secundari de dysfunction sinistro-ventricular. Iste classification es in bon accordo con le classification pathologic de Edwards.[9] Le lesion fundamental pare esser un disturbation del function myocardial con un causa que ha non ancora essite determinate. In commun con altere autores[5, 7] nos prefere le termino "idiopathic hypertrophia cardiac typo I e typo II" al termino "fibroelastosis endocardial."

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# Evaluation of Electrocardiographic Diagnosis of Ventricular Hypertrophy Based on Autopsy Comparison

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RECENT advances in the field of cardiac surgery require greater precision in the diagnosis of early ventricular hypertrophy. Although many electrocardiographic criteria are proposed for the diagnosis of ventricular hypertrophy, only a few articles discuss their accuracy. Most studies apply criteria to either left or right ventricular hypertrophy as found in proved hypertrophy, but sufficient studies of the occurrence of false positives are lacking. It is the object of this study to analyze various criteria for ventricular hypertrophy, as found in isolated hypertrophy and in normal hearts.

## Method

Five hundred and twelve consecutive cases autopsied between January 1954 and October 1956, at the City of Hope Medical Center, were studied. Excluded were cases under the age of 15, those in which an electrocardiogram had not been taken within 3 months prior to death, and those with myocardial infarction, myocardial fibrosis, advanced coronary sclerosis, or definite evidence of myocardial bleeding. Sixty-five cases remained for this study. Thirty-two had anatomically normal hearts, 17 had isolated left ventricular hypertrophy, and 16 had isolated right ventricular hypertrophy (table 1). The thickness of the ventricular wall was used as the indication of ventricular hypertrophy. According to Saphir,[15] the thickness of the normal left ventricular wall should not exceed 10 mm. and that of the normal right ventricular wall should not exceed 3 mm. We considered a heart as normal when the thickness of the left ventricle was 10 mm. or less and the thickness of the right ventricular wall was 3 mm. or less. We classified as isolated left ventricular hypertrophy a heart in which the thickness of the left ventricular wall was 13 mm. or more and the thickness of the right ventricular wall was 3 mm. or less. We used the term isolated right ventricular hypertrophy when the thickness of the right ventricular wall was 5 mm. or more and the thickness of the left ventricular wall was 10 mm. or less. All patients had electrocardiograms consisting of the standard limb leads, the augmented unipolar limb leads, the standard unipolar chest leads, ($V_{1-6}$) and the right precordial leads $V_{4R}$ and $V_{5R}$. A direct-writing electrocardiographic machine was utilized with routine standardization. Upward deflections were measured from the top of the base line to the peak of the upstroke, and downward deflections were measured from the bottom of the base line to the nadir of the downstroke. The T-P level was used as the base line; when tachycardia made it impossible to measure the correct T-P level, the P-R segment was used as the base line. The time of onset of the intrinsicoid deflection in unipolar chest leads was measured from the beginning of the QRS to the top of the R, or to $R_1$, if present. The criteria studied for left ventricular hypertrophy were those of Gubner and Ungerleider;[2] Katz;[3] Schach, Rosenbaum, and Katz;[4] Goldberger;[5, 6] Goulder and Kissane;[7] Noth, Myers, and Klein;[8] Wilson and co-workers;[9–11] and Sokolow and Lyon.[12]

The criteria used by these authors is listed below.

*A. Left Ventricular Hypertrophy*

I. Gubner and Ungerleider[2]
- a) Left axis deviation, with $R_1 + S_3$ exceeding 25 mm.
- b) Left axis deviation with depression of $ST_1$ of 0.5 mm. or more.
- c) Left axis deviation, with $T_1$ of less than 1 mm.

[Note: Left axis deviation signifies that the maximum QRS is located between +30 and –90 degrees.]

II. Katz[3]
- a) 1. Left axis deviation.
  2. ST-T normal. Lead II has small, equiphasic QRS or deep S.
- b) 1. Left axis deviation.
  2. Depressed, upward-convexed S-T and inverted T wave in lead I.
- c) 1. Left axis deviation.

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**Table 1**

*Age Distribution of the Cases*

| Age (yrs.) | Normal | | Left ventricular hypertrophy | | Right ventricular hypertrophy | |
|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female |
| 15—20 | 0 | 1 | 0 | 0 | 1 | 1 |
| 21—30 | 2 | 1 | 0 | 0 | 1 | 1 |
| 31—40 | 3 | 3 | 1 | 1 | 0 | 2 |
| 41—50 | 2 | 3 | 1 | 2 | 3 | 1 |
| 51—60 | 6 | 2 | 1 | 1 | 1 | 0 |
| 61—70 | 3 | 6 | 5 | 0 | 2 | 1 |
| 70 and over | 0 | 0 | 2 | 3 | 2 | 0 |
| Total | 16 | 16 | 10 | 7 | 10 | 6 |

2. Lead II shows a small equiphasic QRS or deep S wave.
3. Lead I shows the ST-T changes such as those seen in *b*.

d) 1. QRS waves are concordant in standard limb leads.
2. Depressed S-T and inverted T wave in lead I and depressed S-T in II, III.

e) 1. $CF_2$ shows QS pattern or an R wave of less than 1.5 mm., S-T elevation of more than 2.5 mm., and upward T wave.
2. $CF_5$ shows a depression of S-T segment and inversion of T wave.

[Note: We used the V lead instead of CF lead. S-T was considered depressed when it was 0.5 mm. or more below the isoelectric line.]

III. Schaeh, Rosenbaum, and Katz[4]

a) Main negative deflection in $aV_R$ more than 14 mm.

b) R wave more than 12 mm. in $aV_L$ (horizontal electrical position) R wave more than 19 mm. in $aV_F$ (vertical electrical position).

c) Sum of the main negative deflection in $aV_R$ and the positive deflection in $aV_L$ or $aV_F$ exceeds the maximum found normally in the respective "electrical" position, (29 mm. in vertical heart, 23 mm. in semivertical heart, 26 mm. in intermediate position of the heart, 22 mm. in semihorizontal heart, and 21 mm. in horizontal heart.)

IV. Goldberger[5]

a) High voltage of QRS complex.
1. In horizontal heart, the R wave 13 mm. or more in $aV_L$.
2. In vertical heart, the R wave of 20 mm. or more in $aV_F$.

b) Left ventricular strain.
Depression of S-T segment of 0.5 mm. or more or inverted T waves in $aV_L$ in horizontal heart, or in $aV_F$ in vertical heart. Depression of S-T segment of 0.5 mm. or more in $V_5$ and $V_6$ or inversion of T waves in $V_5$ and $V_6$.

c) Left ventricular hypertrophy and strain: a combination of *a* and *b*.

V. Goulder and Kissane[7]

a) In horizontal or semihorizontal heart, R wave in $aV_L$ more than 11 mm., with or without a T:R ratio of less than 10 per cent.

b) In horizontal or semihorizontal heart, an R wave of 10 mm. with a T:R ratio of less than 10 per cent.

VI. Noth, Myers, and Klein[8]

a) Time interval from the onset of QRS to peak of R is 0.05 second or more in $V_5$ and $V_6$.

b) Time interval from the onset of R to its peak is 0.04 second or more in $V_5$ and $V_6$.

VII. Wilson and co-workers[9–11]

a) Absence of R wave or abnormally small R wave in $V_1$ (1 mm. or less). Abnormally large S wave in $V_1$ (24 mm. or more).

b) Left shift of transitional zone.
[Note: In our study this placed the transitional zone in $V_5$ or $V_6$.]

c) Delay of peak of R in $V_5$ and $V_6$ (0.05 second or more).

d) Abnormally tall R wave (33 mm. or more in $V_5$, 26 mm. or more in $V_6$).

e) Inverted T wave in $V_5$ and $V_6$.

f) QRS interval of 0.10 or 0.11 second.

VIII. Sokolow and Lyon[12]

a) Standard limb leads
1. Voltage $R_1 + S_3 = 25$ mm. or more.
2. RS-$T_1$ depressed 0.5 mm. or more.
3. $T_1$ flat, diphasic, or inverted, particularly when associated with (2) and a prominent R wave.
4. $T_2$ and $T_3$ diphasic or inverted in the presence of tall R waves and (2).
5. $T_3$ greater than $T_1$ in the presence of left axis deviation and high voltage QRS complex in leads I and III.

b) Precordial leads
1. Voltage of R wave in $V_5$ or $V_6$ exceeds 26 mm.
2. RS-T segment depressed more than 0.5 mm. in $V_4$, $V_5$, or $V_6$.

3. A flat, diphasic, or inverted T wave in leads $V_4$ through $V_6$ with normal R and small S waves and (2).
4. Ventricular activation time in $V_5$ or $V_6$ 0.06 second or more, especially when associated with a tall $R_1$ wave.

c) Unipolar limb leads
1. RS-T segment depressed more than 0.5 mm. in $aV_L$ or $aV_F$.
2. Flat, diphasic, or inverted T wave, with an R wave of 6.0 mm. or more in $aV_L$ or $aV_F$ and (1).
3. Voltage of R wave in $aV_L$ exceeds 10.0 mm.
4. Upright T wave in VR.

In addition to these they found that the ratio of $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ was below 100 (mean 32.0) in normal cases, but found above 100 (mean 98.0) in 33 per cent of the cases of left ventricular hypertrophy in which this ratio could be determined. Therefore, we also added this ratio of above 100 into the criteria of Sokolow and Lyon. The term flat T was used when the amplitude of the T wave in lead I was 1 mm. or less, or R:T ratio was 10 or less in lead $aV_L$, $aV_F$, $V_4$, $V_5$, and $V_6$.

The criteria for right ventricular hypertrophy studied were those of Sokolow and Lyon;[13] Myers, Klein, and Stofer;[14] and Goldberger.[6]

*B. Right Ventricular Hypertrophy*

I. Sokolow and Lyon[13]

a) Voltage of the R and S waves and various ratios:
1. The R wave in $V_1$ is 7.0 mm. or more.
2. The S wave in $V_1$ is less than 2.0 mm.
3. The S wave in $V_5$ or $V_6$ is 7.0 mm. or more.
4. The sum of the amplitudes of the R wave in $V_1$ and the S wave in $V_5$ and $V_6$ exceeds 10.5 mm., in individuals over 5 years of age.
5. The R wave in $V_5$ or $V_6$ is less than 5.0 mm.
6. The ratio of the R to the S wave in $V_5$ or $V_6$ is 1.0 or less.
7. The R wave in $aV_R$ is 5.0 mm. or more.
8. The ratio of $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ is 0.4 or less.
9. The ratio of the R wave in $V_1$ to the S wave in $V_1$ exceeds 4.0 in individuals under the age of 5.
10. The ratio of the R wave to the S wave in $V_1$ exceeds 1.0 in individuals over the age of 5 years.

b) Delayed onset of the intrinsicoid deflection (delayed ventricular activation time) 0.04 to 0.07 second in $V_1$ or $V_2$, or in both.

c) Depression of the RS-T segment and inversion of T wave in:
1. $V_1$, less often $V_2$ and $V_3$ when the R wave equals or exceeds 5.0 mm.
2. $aV_L$ or $aV_F$ when the R wave equals or exceeds 5.0 mm.

d) Marked right axis deviation, greater than 110 degrees suggests, but is not in itself diagnostic of, right ventricular hypertrophy. [Note: Their subjects included 40 per cent infants under the age of 5. The cases in which $V_1$ showed M-shaped QRS complexes with prominent R wave and a ventricular activation time exceeding 0.07 second in lead $V_1$ were all excluded.]

II. Myers, Klein, and Stofer[14]

They studied the 40 cases of preponderant right ventricular hypertrophy proved by autopsy, and classified them into the following 6 groups. Among these cases lead $V_{3R}$ was taken in 8 cases. The unipolar limb leads were taken in 35 cases. Electrocardiograms diagnostic for right ventricular hypertrophy are as follows:

a) 1. Reversal in the R/S ratio in $V_1$ and $V_6$ characterized by an abnormally large R in contrast to S in $V_1$, a diminution in ratio in leads further to the left, and a prominent S in $V_6$.
2. The delay of the time of the onset of the intrinsicoid deflection in $V_1$ (generally between 0.03 and 0.05 second) and greater than in $V_5$ or $V_6$.
3. Tendency to a small Q wave in $V_1$.
4. Tendency to inversion of the T wave in $V_1$ and to upright T wave in $V_6$.
5. QRS interval of less than 0.12 second.
6. Absence of notching or double peaking of the R wave in lead $V_1$.

b) Typical pattern of right ventricular hypertrophy or incomplete right bundle-branch block in lead $V_{3R}$.

c) Right ventricular hypertrophy is presumed from lead $V_6$ and $aV_R$ without confirmatory signs in $V_1$ or $V_2$: abnormally large S wave in $V_6$ with an abnormally tall R in $aV_R$, which was 4 to 10 times the amplitude of the downward deflection in the same lead.

III. Goldberger[6]

a) Atrial hypertrophy (large biphasic P in

**Table 2**

*Criteria of Gubner and Ungerleider for Left Ventricular Hypertrophy*

| | Number of cases | Left axis deviation | | | | |
|---|---|---|---|---|---|---|
| | | $R_{III} + S_{II}$ 25 mm. ∧ | $ST_I$ → 0.5 mm. ∧II | $T_I$ ↓ 1 mm. ∨ | + | − |
| Normal | 32 | 0 | 1 | 6 | 6 | 26 |
| LVH | 17 | 1 | 4 | 5 | 6 | 11 |
| RVH | 16 | 0 | 0 | 0 | 0 | 16 |

$V_1$, $V_2$, or $aV_R$, 0.11 second or more wide, 2.5 mm. or more tall.)

If $aV_R$ in these cases shows a QR or QR pattern, and if $aV_R$ revealed rS pattern, and if lead $aV_L$ showed rS, or QR and downward T, right ventricular hypertrophy can be suspected.

b) Marked clockwise rotation.
   1. If $V_1$ through $V_6$ shows rS pattern and R/S in $V_5$ or $V_6$ is ½ or less.
   2. If $aV_R$ shows qR pattern and R is 3 or more times higher than q.

c) Extreme clockwise rotation; $aV_R$, $V_1$ show qR pattern and inverted T wave.

d) Tall R in $V_1$, or $V_1$ and $V_2$ (R is 3 or more times larger than the s). QRS interval is less than 0.12 second. $V_5$ and $V_6$ show rS pattern.

e) Right bundle-branch block.

We applied these criteria of both left ventricular and right ventricular hypertrophy to all our cases. We considered a positive finding, the presence of one or more of those criteria set forth by the authors above.

## Results

### A. Criteria for the Diagnosis of Left Ventricular Hypertrophy

I. Gubner and Ungerleider[2] (table 2)

a) Of 17 cases with left ventricular hypertrophy, 6 were positive, and 11 were false negatives.

b) There were no false positives among the 16 cases of right ventricular hypertrophy.

c) Among the 32 normal hearts there were 6 false positives. mostly due to the presence of left axis deviation with flat $T_1$ of less than 1 mm.

II. Katz[3] (table 3)

a) Only 7 of the 17 cases with left ventricular hypertrophy were positive, 10 being false negatives.

b) Three of the 16 cases of right ventricular hypertrophy yielded false positives for left ventricular hypertrophy.

c) Among the 32 normal hearts there were 10 false positives for left ventricular hypertrophy.

III. Schach, Rosenbaum and Katz[4] (table 4)

a) Two of 17 cases of left ventricular hypertrophy were positive, leaving 15 cases of false negatives.

b) One false positive was present among the 32 normal cases.

c) There were no false positives among the cases of right ventricular hypertrophy.

IV. Goldberger[5] (table 5)

a) Of 17 cases of proved left ventricular hypertrophy only 6 were positive. If the cases in which digitalis were used are excluded, only 2 of 13 cases were positive.

b) Of 32 normal cases there were 6 false positives for left ventricular hypertrophy.

c) Among the cases of right ventricular hypertrophy there were 3 false positives for left ventricular hypertrophy.

V. Goulder and Kissane[7] (table 6)

a) Only 2 of the 17 cases of left ventricular hypertrophy were positive. If the cases in which digitalis was used are excluded only 1 of 13 cases were positive.

b) There were 4 false positives among the normal cases.

c) There were no false positives among the cases of right ventricular hypertrophy.

VI. Noth, Myers, and Klein[8] (table 7)

a) Three of the 17 cases of left ventricular hypertrophy were positive. If the cases in which digitalis was used are excluded, 2 of 13 cases are found to be positive.

b) One of the 32 normal cases was positive.

c) There were no false positives among the cases of right ventricular hypertrophy.

**Table 3**

*Criteria of Katz for Left Ventricular Hypertrophy*

| | Number of cases | Left axis deviation: IIRS, vS ST-T normal | Left axis deviation: $ST_1\downarrow$ $T_1\downarrow$ | Left axis deviation: II RS, vS ST-$T_1$ | QRS concordant RS-T I (II, III)↓ | $CF_2$ ($V_2$):QS or v <1.5 mm. ST↑ >2.5 mm. T↑ | $CF_2$ ($V_5$) ST-T↓ | + | − |
|---|---|---|---|---|---|---|---|---|---|
| Normal | 32 | 7 | 2 | 1 | 1 | 0 | 0 | 10 | 22 |
| LVH | 17 | 3 | 2 | 0 | 0 | 0 | 4 | 7 | 10 |
| RVH | 16 | 0 | 0 | 0 | 1 | 0 | 2 | 3 | 13 |

VII. Wilson and co-workers[9-11] (table 8)

a) Sixteen of the 17 cases of left ventricular hypertrophy were positive. If the cases in which digitalis was given are excluded then only 5 of 13 cases are found to be positive.

b) False positives were found among 25 of the 32 normal cases.

c) Twelve of the 16 cases of right ventricular hypertrophy were false positives. According to Scott and his co-workers,[15, 16] the presence of a Q wave in $V_5$ and $V_6$ is included in the above mentioned criteria. However, this is not reasonable because small Q waves are usually seen in the left-sided chest leads in normal subjects. If we exclude the Q waves, only 7 of the 17 cases of left ventricular hypertrophy are positive and the false positives are reduced to 14 in the normal cases and 7 in the cases of right ventricular hypertrophy. Furthermore, if we eliminate the cases in which digitalis was given then the false positives are only 13 of the 32 cases among the normal subjects and 6 of 13 cases of right ventricular hypertrophy.

VIII. Sokolow and Lyon[12, 13] (tables 9, 10, 11, and 12)

a) Fifteen of 17 cases of left ventricular hypertrophy were positive.

b) There were 17 false positives among the 32 normal subjects.

c) There were 10 false positives among 16 cases of right ventricular hypertrophy.

**Table 4**

*Criteria of Schach, Rosenbaum, and Katz for Left Ventricular Hypertrophy*

| | Number of cases | $aV_R$ main neg. deflection >14 mm. | R $aV_L$> 19 mm.* R $aV_L$ >12 mm† | Neg. $aV_R$ + pos. $aV_L$ or $aV_F$ >max. normal | + | − |
|---|---|---|---|---|---|---|
| Normal | 32 | 0 | 1 | 1 | 1 | 31 |
| LVH | 17 | 1 | 0 | 1 | 2 | 15 |
| RVH | 16 | 0 | 0 | 0 | 0 | 16 |

*Vertical electrical position.

†Horizontal electrical position.

**B. Criteria for the Diagnosis of Right Ventricular Hypertrophy**

I. Myers, Klein, and Stofer[14] (table 13)

a) Eight of 16 cases of right ventricular hypertrophy were positive.

b) One false positive was found among the 32 normal hearts.

c) One false positive occurred in the 17 cases of left ventricular hypertrophy.

d) If the cases in which digitalis was used are omitted, then where were 6 positives among the 14 cases of right ventricular hypertrophy and no false positives among the cases of left ventricular hypertrophy.

II. Sokolow and Lyon[12, 13] (table 14)

a) Twelve positives were present among the 16 cases of right ventricular hypertrophy.

b) Sixteen false positives were found in the 32 normal subjects.

**Table 5**

*Criteria of Goldberger for Left Ventricular Hypertrophy*

| | Number of cases | Horizontal: R $aV_L$ ≧13 mm. | Horizontal: ST $aV_L$↓ or T $aV_L$↓ | Vertical: R $aV_F$ ≧20 mm. | Vertical: ST-T $aV_F$↓ | ST-T $V_5$, $V_6$↓ 0.05 mm. or T↓ | + | − |
|---|---|---|---|---|---|---|---|---|
| Normal | 32 | 1 | 0 | 0 | 0 | 6 | 6 | 26 |
| LVH | 17 | 0 | 0 | 0 | 0 | 6 | 6 | 11 |
| RVH | 15 | 0 | 0 | 0 | 0 | 3 | 3 | 12 |

**Table 6**

*Criteria of Goulder and Kissane for Left Ventricular Hypertrophy*

| | No. of cases | R $aV_L$ >11 mm. | R $aV_L$ = 10 or 11 mm. T/R $aV_L$<0.1 | + | − |
|---|---|---|---|---|---|
| Normal | 32 | 2 | 2 | 4 | 28 |
| LVH | 17 | 2 | 0 | 2 | 15 |
| RVH | 16 | 0 | 0 | 0 | 16 |

**Table 7**

*Criteria of Noth, Myers, and Klein for Left Ventricular Hypertrophy*

| | Number of cases | $V_5$ and $V_6$: R intrinsicoid deflection ≧0.04 | $V_5$ and $V_6$: qR intrinsicoid deflection ≧0.05 | + | − |
|---|---|---|---|---|---|
| Normal | 32 | 1 | 0 | 1 | 31 |
| LVH | 17 | 1 | 2 | 3 | 14 |
| RVH | 16 | 0 | 0 | 1 | 16 |

c) Four of 16 cases of left ventricular hypertrophy were positive.

d) If the cases in which digitalis was given are excluded, there are 10 positives among the 14 cases of right ventricular hypertrophy, 16 false positives in the 31 normal hearts and 4 of 12 cases of left ventricular hypertrophy.

III. Goldberger[5, 6] (table 15)

a) There were 11 positives among the 16 cases of right ventricular hypertrophy.

b) Two false positives in the 32 normal subjects were found.

c) Five of the 17 cases of left ventricular hypertrophy were positive. Note: These criteria include atrial hypertrophy (0.11 second or more wide or 2.5 mm. or more tall) but this is an indirect sign. If this is omitted, only 6 positives occurred among the 16 cases of right ventricular hypertrophy with 2 false positives in the normal subjects and 1 of the 2 cases of left ventricular hypertrophy.

d) If the cases in which digitalis was used are excluded, there are 9 positives among 14 cases of right ventricular hypertrophy, 2 false positives among 3 normal subjects and 2 of 13 cases of left ventricular hypertrophy. If the criteria of atrial hypertrophy is omitted in addition, then there are 4 positives among 14 cases of right ventricular hypertrophy.

## Discussion

Electrocardiography is a diagnostic means to estimate a state of myocardium by analyzing the action current produced by heart muscle. Therefore, an electrocardiogram is an electrodynamic expression of the function of heart muscle, not a pathologic, static expression. Even the tension of the muscle fibers of the heart may change the electrocardiographic findings.[17] It is well known that there is a discrepancy between the anatomic position of the heart and the electrical axis of the heart defined by electrocardiograms.[18] Therefore, some disagreement between anatomic and electrocardiographic findings is inevitable.

Compared to the days in which only the standard limb leads were used, the clinical application of the unipolar limb and multipl

**Table 8**

*Criteria of Wilson and His Co-workers for Left Ventricular Hypertrophy*

| | | $V_1$ | | | $V_5$ | | | | $V_6$ | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number of cases | R≤1 mm. | S≥4 mm. | Transit. zone shifts to left | Q+ | R≥3 mm. | Intrinsicoid deflection ≥0.05 sec. | T↓ | Q+ | R≥6 mm. | Intrinsicoid deflection ≥0.05 sec. | T↓ | QRS 0.10 to 0.11 | + | − |
| Normal | 32 | 11 | 0 | 1 | 15 | 0 | 0 | 0 | 21 | 0 | 0 | 2 | 1 | 25 | 7 |
| LVH | 17 | 3 | 0 | 1 | 10 | 1 | 2 | 2 | 15 | 1 | 2 | 1 | 3 | 16 | 1 |
| RVH | 15 | 0 | 0 | 2 | 3 | 0 | 0 | 2 | 5 | 0 | 0 | 1 | 4 | 12 | 3 |

**Table 9**

*Criteria of Sokolow and Lyon for Standard Limb Leads for Left Ventricular Hypertrohpy*

| | | | | RS-$T_1$↓ ≧ 0.5 mm. | | | | |
|---|---|---|---|---|---|---|---|---|
| | Number of cases | $R_1 + S_3$ ≧25 mm. | RS-$T_1$↓ ≧0.5 mm. | prominent R diphasic $T_1$ inverted flat | tall R II, III diphasic T II, III inverted | Left axis deviation high voltage (I, III) $T_3 > T_1$ | + | − |
| Normal | 32 | 0 | 2 | 1 | 0 | 3 | 4 | 28 |
| LVH | 17 | 1 | 5 | 5 | 1 | 2 | 6 | 11 |
| RVH | 16 | 0 | 2 | 1 | 1 | 0 | 2 | 14 |

chest leads made clinical electrocardiography much more accurate. Concomitantly, the accurate determination of ventricular hypertrophy has become important in clinical medicine. In advanced cases of ventricular hypertrophy, the diagnosis may be made easily by x-ray or by physical examination. In less advanced cases, however, which usually occur in the early stages of cardiovascular diseases, the accurate diagnosis of ventricular hypertrophy is often difficult by these means. The electrocardiographic method has been used to detect early pathologic changes of myocardium. There are many criteria for the diagnosis of the ventricular hypertrophy proposed by different authors[2-10, 12-14] but there are only a few papers[15, 16] about the comparative study of these criteria. Good criteria for the diagnosis of ventricular hypertrophy should have a good positivity and few or no false positives.

Scott et al.[15] studied 100 cases of pure left ventricular hypertrophy proved by autopsy. They concluded that the criteria of Sokolow and Lyon, Wilson et al., Goldberger, and Katz give, in order, the most accurate electrocardiographic diagnosis of left ventricular hypertrophy, obtaining 85 per cent accuracy using Sokolow and Lyon's criteria. They did not, however, determine the occurrence of false positives. As shown in table 16, the occurrence of false positives is important in the evaluation of these criteria. In the application of these criteria, cases that show one or more of the items listed in each table were considered positive, as Scott et al. did. There are 2 criteria (i.e., those of Wilson, and of Sokolow and Lyon) that show a high correlation with

**Table 10**

*Criteria of Sokolow and Lyon for Unipolar Limb Leads for Left Ventricular Hypertrophy*

| | Number of cases | T $aV_R$↑ | $aV_L$ R>11 mm. | $aV_L$ ST-T >0.5 mm. | $aV_L$ T low or ↓ + R≧6 mm. TRS-T↓ | $aV_F$ R>20 mm. | $aV_F$ RS-T↓ >0.5 mm. | $aV_F$ T low or ↓ + R≧6 mm. TRS-T↓ | + | − |
|---|---|---|---|---|---|---|---|---|---|---|
| Normal | 32 | 0 | 2 | 2 | 2 | 0 | 3 | 0 | 6 | 26 |
| LVH | 17 | 1 | 2 | 1 | 1 | 0 | 5 | 2 | 7 | 10 |
| RVH | 16 | 0 | 0 | 1 | 0 | 0 | 5 | 2 | 5 | 11 |

**Table 11**

*Criteria of Sokolow and Lyon for Unipolar Chest Leads for Left Ventricular Hypertrophy*

| | Number of cases | $V_5$ R>26 mm. | $V_5$ RS-T↓ >0.5 mm. | $V_5$ T low or ↓ | $V_5$ Intrinsicoid deflection ≧0.05 sec. | $V_6$ R>26 mm. | $V_6$ RS-T↓ >0.5 mm. | $V_6$ T low or ↓ | $V_6$ Intrinsicoid deflection ≧0.05 sec. | R/T $V_5$ ≧0.1 | R/S in $V_5$ / R/S in $V_1$ >100 | RV5, V6 / S $V_1$ >35 mm. | + | − |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Normal | 32 | 0 | 1 | 2 | 0 | 0 | 2 | 0 | 0 | 9 | 5 | 0 | 14 | 18 |
| LVH | 17 | 2 | 3 | 3 | 1 | 0 | 4 | 1 | 1 | 10 | 4 | 6 | 13 | 4 |
| RVH | 15 | 1 | 4 | 4 | 0 | 0 | 1 | 1 | 0 | 6 | 0 | 1 | 8 | 7 |

**Table 12**

*Criteria of Sokolow and Lyon for Left Ventricular Hypertrophy*

| | Standard limb leads only | Standard limb leads + AV | Standard limb leads + AV + chest leads | + | − |
|---|---|---|---|---|---|
| Normal | 4 | 9 | 17 | 17 | 15 |
| LVH | 7 | 10 | 15 | 14 | 3 |
| RVH | 1 | 5 | 10 | 10 | 5 |

the diagnosis of left ventricular hypertrophy. However, if the presence of Q wave in leads $V_5$ and $V_6$ are excluded from Wilson's criteria, the correlation with left ventricular hypertrophy decreases markedly. Sokolow and Lyon's criteria, when applied to our normal cases and the cases of pure right ventricular hypertrophy, had a high rate of false positives. From this point of view each item of the criteria was reviewed. If the items causing a high incidence of false positives, listed below, are omitted from the criteria, the positivity for left ventricular hypertrophy is 71 per cent (12 of 17 cases) and the false positives are 19 per cent (6 of 32 cases) in the normal subjects and 13 per cent (2 of 16 cases) in pure right ventricular hypertrophy.

The items responsible for a high incidence of false positives are as follows:

1. Depression of RS-T segment in lead I more than 0.5 mm.
2. Depression of RS-T segment in lead $aV_L$ or $aV_F$ over 0.5 mm.

**Table 13**

*Criteria of Myers, Klein, and Stofer for Right Ventricular Hypertrophy*

| | | A | B | C | D | E | | |
|---|---|---|---|---|---|---|---|---|
| | Number of cases | Reversal of R/S in $V_1$, $V_6$ I.D.* of $V_1$ 0.03 0.05 I.D. of $V_1$ $\wedge$ $V_6$ $V_1 = Q$ | $V_{2R} = RVH$ incomplete RBBB $V_1$, $V_2$, neg. | $V_6$, $aV_R =$ RVH suggestive $V_1$, $V_2$ neg. | Incomplete RBBB | Complete RBBB | + | — |
| Normal | 32 | 0 | 1 | 0 | 0 | 0 | 1 | 31 |
| LVH | 17 | 0 | 0 | 0 | 1 | 0 | 1 | 16 |
| RVH | 16 | 4 | 2 | 0 | 2 | 0 | 8 | 8 |

*Intrinsicoid deflection.

**Table 14**

*Criteria of Sokolow and Lyon for Right Ventricular Hypertrophy*

| | Number of cases | $RV_1 \geq$ 17 mm. | $SV_1 \leq$ 2 mm. | $SV_5$, $V_6 \geq$ 7 mm. | $RV_1 + SV_5$, $V_5 \geq$ 10.5 mm. | $RV_5$, $V_6 \leq$ 5 mm. | R/S $V_5$, $V_6 \leq$ 1 | R $aV_R \geq$ 5 mm. | R/S in $V_6$ / R/S in $V_1 \leq$ 0.4 | R/S in $V_1 \geq$ 1 | Intrinsicoid deflection, $V_1$ 0.04 $\geq$ | $TV_1 + RV_1 \geq$ 5 mm. | Right axis deviation $\geq$ 110 deg. | + | — |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Normal | 32 | 1 | 3 | 0 | 1 | 10 | 1 | 0 | 0 | 2 | 1 | 0 | 1 | 16 | 16 |
| LVH | 16 | 0 | 0 | 1 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 12 |
| RVH | 16 | 2 | 4 | 4 | 4 | 6 | 6 | 3 | 1 | 1 | 7 | 4 | 8 | 12 | 4 |

3. Criterion 2 and flat, diphasic, or inverted T wave with R wave of over 6 mm.
4. Depression of RS-T segment in leads $V_4$, $V_5$, and $V_6$ over 0.5 mm.
5. Criterion 4 and flat, diphasic, or inverted T wave with Rs pattern.
6. R/T ratio of more than 10 in leads $V_5$ and $V_6$.
7. R/S in $V_5$ ratio of more than 100.
8. $\frac{\text{R/S in } V_6}{\text{R/S in } V_1}$

Generally speaking, the changes of the RS-T segment and of the T wave show a high incidence of false positives when used as a criterion of left ventricular hypertrophy. Myocardial ischemia of varying etiology and electrolyte imbalance, which is observed in many conditions especially near terminus, will be causes of this false positivity.

**Table 15**

*Criteria of Goldberger for Right Ventricular Hypertrophy*

| | Number of cases | Atrial hypertrophy | Marked clockwise rotation | Extreme clockwise rotation | Tall $RV_1$ (2) T $\downarrow$ | Right bundle-branch block | + | — |
|---|---|---|---|---|---|---|---|---|
| Normal | 32 | 0 | 0 | 0 | 0 | 2 | 2 | 30 |
| LVH | 17 | 4 | 0 | 0 | 0 | 1 | 5 | 12 |
| RVH | 16 | 6 | 0 | 4 | 1 | 2 | 11 | 5 |

In right ventricular hypertrophy, Walker

**Table 16**

*Positivity and False Positivity of Criteria for Ventricular Hypertrophy*

| | Number of cases | Normal 32 | | Isolated LVH 17 | | | Isolated RVH 16 | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Number of pos. cases | % | Number of pos. cases | % | Scott et al. (%) | Number of pos. cases | % | Walker et al (% |
| Criteria for LVH | Gubner, Ungerleider | 6 | 18.8 | 6 | 35.3 | 36.0 | 0 | 0 | |
| | Katz | 10 | 31.3 | 7 | 41.2 | 59.0 | 3 | 18.8 | |
| | Schach, Rosenbaum, Katz | 1 | 3.1 | 2 | 11.8 | 21.9 | 0 | 0 | |
| | Goldberger | 6 | 18.8 | 6 | 35.3 | 68.0 | 3† | 20.0 | |
| | Goulder, Kissane | 4 | 12.5 | 2 | 11.8 | 27.0 | 0 | 0 | |
| | Noth, Myers, Klein | 1 | 3.1 | 3 | 17.6 | 28.0 | 0 | 0 | |
| | Wilson | 25 | 78.1 | 16 | 94.1 | 81.0 | 12† | 80.0 | |
| | | (14)** | (43.8) | (17) | (41.2) | | (7) | (46.7) | |
| | Sokolow, Lyon | 17 | 53.1 | 15 | 88.2 | 85.0 | 10† | 66.7 | |
| Criteria for RVH | Myers, Klein, Stofer | 1 | 3.1 | 1 | 5.9 | | 8 | 50.0 | 13.6 |
| | Sokolow, Lyon | 16 | 50.0 | 4‡ | 25.0 | | 12 | 75.0 | 22.7 |
| | Goldberger* | 2 | 6.3 | 5 | 29.4 | | 11 | 68.7 | |

*Result when the atrial hypertrophy was omitted.

†Number out of 15 cases.

‡Number out of 16 cases.

**Figures in parentheses are result when the presence of Q wave in Lead $V_5$ and $V_6$ was omitted.

et al.[16] reported that they found only 23 per cent (5 of 22 cases) positivity using Sokolow and Lyon's criteria and 14 per cent (3 of 22 cases) positivity by using the criteria of Myers and his co-workers. They concluded that frequently the electrocardiogram will not be diagnostic in the presence of anatomic right ventricular hypertrophy.

In Goldberger's criteria we included the item of atrial hypertrophy (0.11 second or more wide, 2.5 mm. or more tall) as one item of the criteria of right ventricular hypertrophy. If this is omitted, the positivity decreases markedly, as does the false positivity. Sokolow and Lyon's criteria show high positivity (75 per cent) in right ventricular hypertrophy, but also show a high incidence of false positives, 50 per cent (16 of 32 cases) of the normal subjects and 25 per cent (4 of 16 cases) of the cases of the left ventricular hypertrophy. Among each item of Sokolow and Lyon's criteria, the following items are responsible for the high incidence of false positivities:

1. $S V_1 < 2$ mm.
2. $S V_5, V_6 > 7$ mm.
3. $R V_5, V_6 < 5$ mm.
4. $R/S V_5, V_6 < 1$

If these items are omitted from these criteria, the positivity for the diagnosis of right ventricular hypertrophy is 63 per cent (10 of 16 cases) and the false positivity is 9 per cent

(3 of 32 cases) in the normal cases. In this instance there is no false positivity in the cases of left ventricular hypertrophy. The reason for this, a clockwise rotation along its longitudinal axis which is frequently observed normally, is one of the important factors of the false positivity when applying Sokolow and Lyon's criteria.

Myers' criteria show very few false positives, but the positivity for right ventricular hypertrophy is only 50 per cent. Applying these criteria, we strictly followed the criteria for incomplete right bundle-branch block proposed by him; so atypical incomplete right bundle-branch block such as rSr′ pattern in the right-sided chest leads was not considered as significant.

If this kind of incomplete right bundle-branch block is considered as significant, their positivity increases to 88 per cent (14 of 16 cases), but the false positivities increase to 22 per cent (7 of 32 cases) in normal subjects, and 24 per cent (4 of 17 cases) in cases of left ventricular hypertrophy. The reason for this is the heterogeneous origins for incomplete right bundle-branch block as emphasized by Allenstein.[19]

## Conclusions

Several criteria for the diagnosis of left ventricular hypertrophy and right ventricular hypertrophy were studied referring to positivity as well as false positivity.

Criteria for the diagnosis of left ventricular hypertrophy proposed by Gubner, Ungerleider; Katz; Schach, Rosenbaum, and Katz; Goulder and Kissane; and Noth, Myers, and Klein, showed a low incidence of positivity, under 50 per cent. The criteria of Wilson and co-workers, and Sokolow and Lyon, showed relatively high positivities, but they also had a high incidence of false positives. The reason for the high false positivities of these 2 criteria was evaluated.

The criteria for the diagnosis of right ventricular hypertrophy as proposed by Goldberger; Myers, Klein, and Stofer; and Sokolow and Lyon, were studied. They had a high incidence of false positives and a poor incidence of positive correlation.

These findings indicate that great caution must be taken in applying these criteria in clinical practice.


## Summario in Interlingua

Plure criterios electrocardiographic pro le diagnose de hypertrophia sinistro-ventricular e hypertrophia dextero-ventricular esseva studiate con attention prestate al procentages de positivitate si ben como de positivitate false.

Le criterios pro le diagnose de hypertrophia sinistro-ventricular proponite per Gubner e Ungerleider, per Katz, per Schach, Rosenbaum, e Katz, per Goulder e Kissane, e per Noth, Myers, e Klein monstrava un basse incidentia de positivitate, amontante a minus que 50 pro cento. Le criterios de Wilson, Rosenbaum, e Johnston e de Sokolow e Lyon monstrava relativemente alte valores de positivitate, sed illos etiam resultava in un alte incidentia de positivitate false. Le rationes pro le alte false positivitate in iste duo casos es evalutate.

Esseva studiate le criterios pro le diagnose de hypertrophia dextero-ventricular proponite per Goldberger, per Myers, Klein, e Stofer, e per Sokolow e Lyon. Illos ha un alte incidentia de false positivitate e un basse incidentia de correlation positive.

Le constatationes indica que le uso de iste criterios in le practica clinic require le plus meticulose precaution.


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**Pollack, A. A., and Gudger, J. R.: Benign Hypertension.** Arch. Int. Med. 103: 758 (May), 1959.

A study based on data from the files of life insurance policyholders is reported. The persons in question were required to pay increased insurance premium rates because at least one blood pressure reading had been found to be above 136 mm. Hg systolic or 88 mm. Hg diastolic. Otherwise the individuals were in good health. The data offered no evidence that lability of the blood pressure was a significant factor in the moderately increased mortality. The observed fluctuations in blood pressure did not indicate that the life span in these persons was greater than that of persons with constantly observed hypertension. Therefore, it would seem proper to include a proportionate number of elevated readings with the normal ones in the determination of the average blood pressure for an individual person. These data also supported the generally accepted conclusion that the significance of hypertension becomes less important as the age of the person advances. Finally, the results of this study suggested the desirability for early recognition of temporary elevations in blood pressure and their importance in otherwise healthy persons.

KRAUSE

# Preparation of Electrocardiographic Data for Analysis by Digital Electronic Computer

*By* HUBERT V. PIPBERGER, M.D., EDWARD D. FREIS, M.D., LEONARD TABACK, B.E.E., AND HENRY L. MASON, SC.D.

DIGITAL electronic computers are finding increasing applications in the analysis of medical and biologic data. The principal advantages are high speed, relatively great accuracy, and extreme versatility, especially for analytic operations that are too tedious and time-consuming for routine clinical use. Large amounts of data can be processed on a completely objective basis in a relatively short time. Thus computation by commercially available machines should facilitate extensive statistical studies, mass screening of the population, and the data handling of patient records in large organizations such as the Veterans Administration.

The electrocardiogram was chosen for a pilot study in automatic data processing, since it has important clinical applications as a diagnostic aid. The electrical signals from the heart are repetitive and relatively well adapted for objective mathematical treatment. Once the feasibility of the method is established in electrocardiography, only minor modifications of the equipment would be required in other applications such as phonocardiography, ballistocardiography, hemodynamic pressure and flow curves, electroencephalography, and electromyography.

Several efforts have been made in recent years to apply analog computers to the analysis of the electrocardiogram.[1-8] For example, McFee,[1] Sayers et al.,[5] and Abildskov et al.[7] have proposed conversion of signals from 3 orthogonal electrocardiographic leads into curves of spatial magnitude and orientation. Such a conversion does not necessarily lead to automatic analysis, since the newly obtained tracings must be interpreted in fashion similar to the original records. Although a few specific procedures are readily and economically accomplished by analog computation, the examination of large quantities of data for relationships that may never have been precisely formulated seems a task better suited to the digital computer. The problem of interpreting electrocardiographic wave forms is believed to be primarily one of recognition of pattern. Analog devices adapted for this use are likely to be single-purpose, and the probability is strong that a continuing development of equipment would be needed to meet drastic changes of processing procedures.

On the other hand, if the researcher has access to a general purpose digital computer, an almost infinite variety of measurement and analysis can be had merely by writing a new set of instructions for the machine. Then conversion of electrical heart signals to numbers and their storage in a form acceptable to the computers becomes an essential preliminary step. In the present report, a pilot facility for accomplishing this purpose automatically is described.

## Materials and Methods

Three corrected, orthogonal electrocardiographic leads (Schmitt's SVEC III system)[9, 10] were recorded simultaneously on magnetic tape through FM (frequency modulation) channels, with use of a tape recorder.* Differential preamplification with a gain of 1,000 and a frequency response flat from 0.1 to 1,250 c.p.s. was used. A fourth direct (voice) channel permitted recording of verbal information including identification of each

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*Ampex Corporation, Type FR 104.

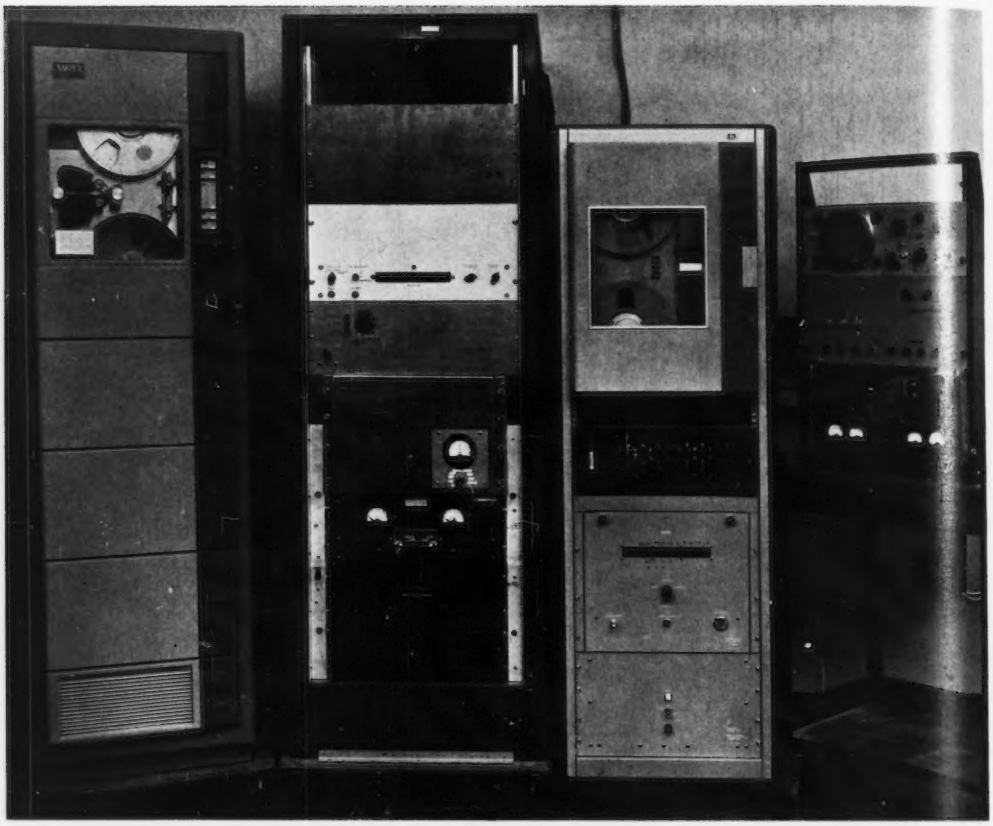
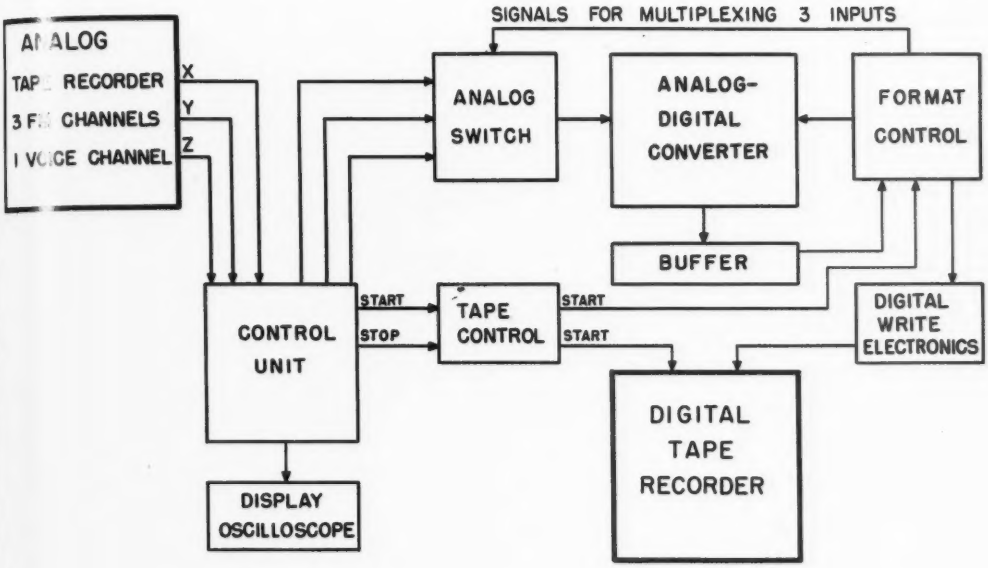


**Figure 1**

*Equipment for the conversion of electrocardiographic data from their original analog into digital form. The control unit with a display oscilloscope is seen on the right. The electrocardiographic signals are retrieved from the analog tape recorder (on the left) and re-recorded through a digital magnetic tape recorder (second from the right, with the analog-to-digital converter in its lower section). The remaining equipment used in the automatic data conversion process is built into the unit which is seen second from the left.*

patient. The electrocardiographic tracings were monitored on a cathode-ray oscilloscope both before and during recording. Calibration was obtained by recording periodically a 2-millivolt peak-to-peak square-wave signal on all 3 FM channels of the tape recorder. Tracings of approximately 20 cardiac cycles from each of about 100 patients have been recorded on each tape reel.

The equipment for conversion of analog-to-digital data was operated by a technician sitting at the control unit (figs. 1 and 2). The electrical heart signals were retrieved as voltages from the magnetic tape by using the play-back mechanism of the analog recorder. The operator examined these records on an oscilloscope screen, a high-speed electronic switch providing him with simultaneous displays of all 3 leads automatically timed to the heart rate and synchronized successively to show similar intervals of as many beats as might be desired. In cases with normal sinus rhythm, each cycle will comprise the familiar P-QRS-T complex. The operator, after viewing several cycles to check the essential uniformity of successive complexes, pressed a "record" switch that initiated the conversion of the next cycle, and monitored it on the oscilloscope. If it appeared to be nontypical (e.g., an extrasystole), he backed up the analog tape drive and recorded an earlier cycle.




**ANALOG TO DIGITAL CONVERSION SYSTEM FOR ELECTROCARDIOGRAPHIC DATA**

**Figure 2**

*Block diagram of the equipment used for the analog-to-digital data conversion for electrocardiograms.*

The remainder of the process was completely automatic, requiring no further manipulations by the operator.

The control unit first sets the digital tape transport into motion. After a brief delay to bring the tape up to proper speed, the format control is activated. This apparatus fulfills several functions: (1) by controlling the analog switch it samples each of the 3 leads X, Y, and Z 1,000 times a second; (2) it initiates the operation of the analog-to-digital converter* which converts the analog voltages to binary digits represented by sets of pulses, and feeds these pulses to a buffer which amplifies them and feeds them back to the format control unit; (3) the latter delivers them serially to the digital "write" electronic unit for recording on digital magnetic tape.

The digital write electronic unit provides proper data form and power level for energizing the "record" heads of the digital tape recorder. At the end of a cardiac cycle the conversion equipment receives a stop signal from the control unit, and is then ready for the next patient's record. Records of 1 cardiac cycle of each of approximately 1,000 patients can be stored on one reel of digital magnetic tape.

The digital tape format was designed to be compatible with one of the digital computers available at the National Bureau of Standards.** Consequently, the information thus stored can be fed directly into any digital computer of this type for further processing and analysis of the electrocardiographic data as may be desired.

### Results

Records of 988 patients with a variety of electrocardiographic abnormalities were processed through the described analog-to-digital conversion equipment and a digital computer.* An obvious test for the proper functioning of the automatic equipment is the conformity between the original records and graphs of the 3 processed electrocardiographic

*Epoco "Datrac."

*IBM Type 704.

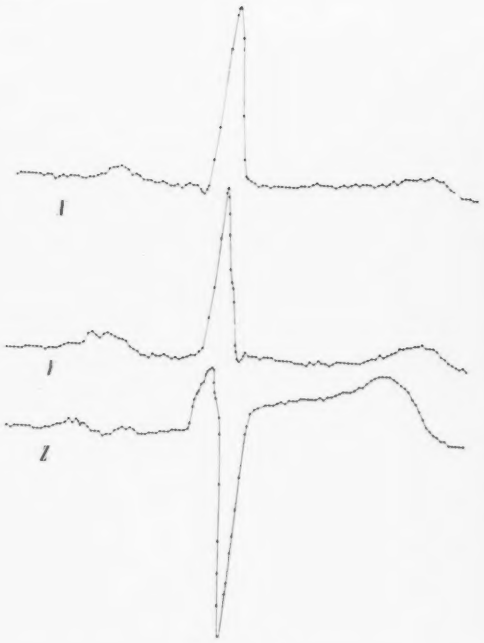



**Figure 3**

*Record shown in figure 4 after processing through conversion equipment and digital computer. The tracing was printed out in numerical form and replotted on the basis of this digital information. Amplitudes, wave forms, and time relationships were maintained satisfactorily. This time scale is expanded more than that of figure 4.*

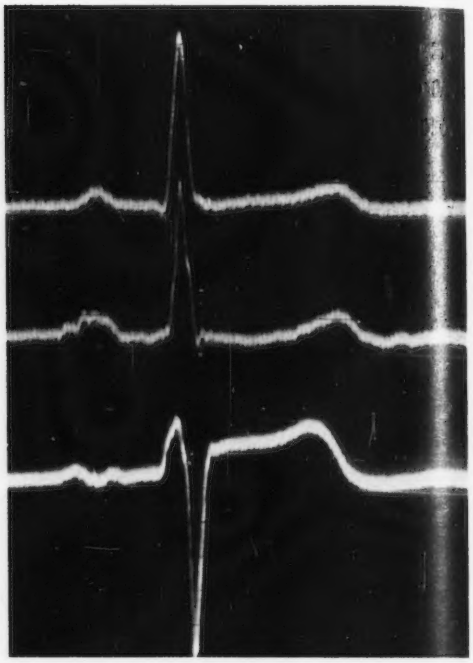


**Figure 4**

*Sample record of 3 orthogonal electrocardiographic leads (X, Y, Z from top to bottom) replayed from analog magnetic tape and photographed from an oscilloscope screen.*

leads on the basis of the digital print-out received from the computer. Figure 3 is a graph of a 3-lead electrocardiogram (patient C-21), after its conversion from the analog record on magnetic tape, its read-in to the digital computer, and its print-out as a column of numbers at millisecond intervals. Except where greater resolution was required accurately to delineate the curve, only every fifth number was plotted. The original electrocardiogram was a sequence of 22 successive beats but the pattern of figure 3 was sufficiently distinctive to permit a single beat to be selected from the original record of 22 cardiac cycles. When the graph was overlaid by the film record of that original, enlarged 12 times as in figure 4, the amplitudes of the 2 diagrams were found to coincide within a trace width—a discrepancy far less than the beat-to-beat variability of an average electrocardiogram. A number of other patients' digitized records, plotted at 10-millisecond intervals, showed equally good correspondence. Thus, it has been demonstrated that the facility used for conversion and digital storage of electrocardiographic data performs satisfactorily and reliably.

## Discussion

As pointed out above, logical and mathematical operations on electrocardiographic data in digital form afford a high degree of flexibility. Once the signals are stored on digital magnetic tape in a suitable format, only proper programming of a digital computer is required to provide a great variety of analytic procedures. This flexibility appears especially important for the establishment of clinical norms and the discovery of new diagnostic

procedures. When these have been tested by experience, a special-purpose computer for electrocardiographic data might then be designed, to replace the general purpose equipment described in this report. The size and cost of the required apparatus might then be brought down within the reach of an average hospital.

Objective data analysis with computers could provide a considerable increase in diagnostic accuracy, since subjective and descriptive criteria for electrocardiographic interpretation can be replaced by quantitative statements. Rather elaborate analytic and statistical procedures take only a few seconds on a digital computer and so pose no major problems. Also the electrocardiographic information can be supplemented by salient facts from the patient's history and physical examination, which can be entered into the digital computer on punched cards. There are no instrumental limitations, therefore, for providing a more broadly based computer program as an aid in electrocardiographic diagnosis. The total information thus available would greatly facilitate statistical correlations of various parameters.

Magnetic tape provides a convenient medium for recording and storing electrocardiographic tracings. The original analog tape can be used at any time for the display of old records either on an oscilloscope in scalar or vectorial form or, if so desired, for re-recording old tracings on paper. Considerably less storage space is required for magnetic tape than for conventional recording media.

The described equipment requires only minor changes to make possible the inclusion of other diagnostic methods for cardiac evaluation. Modifications for phonocardiography, respiratory volume curves, and pulse tracings are presently being made.


## Summary

A pilot facility for automatic processing of electrocardiograms leading to their analysis by digital computer has been described. Wave forms from orthogonal electrocardiographic leads were recorded on magnetic tape. By means of newly designed conversion equipment these records have been converted from their original analog form into digital form. The further processing and analysis of the data thus becomes feasible through the use of commercially available digital electronic computers. It has been demonstrated that the electrocardiographic tracings as recorded from patients can be reproduced from the resulting numerical print-outs in their original and undistorted form. The further analysis of these records then requires only proper programming of a digital computer. The same equipment with minor modifications can be used for automatic processing of other analog data such as phonocardiograms, pulse tracings, and ballistocardiograms.



## Summario in Interlingua

Es describite un arrangiamento de dispositivos pro le manipulation automatic de electrocardiogrammas preparatori a lor analyse per medio de un computator digital. Formas de unda ab orthogone derivationes electrocardiographic esseva registrate in bandas magnetic. Per medio de un novemente elaborate dispositivo de conversion iste registrationes esseva convertite ab lor forma original analoge a in un forma digital. Le cetere processage e le analyse del datos deveni assi effectuabile per le uso de commercialmente disponibile computatores electronic digital. Il ha essite demonstrate que le registrationes electrocardiographic obtenite ab le patientes pote esser reproducite ab le resultante configuration numeric in lor forma original sin ulle distorsion. Le analyse additional de iste registrationes require alora solmente le appropriate programmation del computator digital. Le mesme apparatura con minor modificationes pote esser usate pro le processage automatic de altere datos analoge como per exemplo illos del phonocardiogramma, de registrationes de pulso, e del ballistocardiogramma.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**Dollery, C. T., Harington, M., and Kaufmann, G.: The Mode of Action of Chlorothiazide in Hypertension.** Lancet 1: 1215 (June 13), 1959.

In a series of experiments it was demonstrated that chlorothiazide potentiates the ganglion-blocking agents (as exemplified by pentolinium) by causing a reduction in plasma volume. A negative sodium balance was observed in 11 patients, but the extent of this did not correlate well with the development of increased sensitivity to pentolinium. There was better correlation with the changes in plasma volume. In 8 of 13 patients studied, 3 days' treatment with chlorothiazide produced a fall in plasma volume and all of them showed an increased sensitivity to pentolinium. In 4 out of 5 in whom there was no significant change in plasma volume, the effect of pentolinium was unchanged. Replacement of the calculated loss in plasma volume with salt-free Dextran in 7 patients was followed by reduction in sensitivity to pentolinium to about the pre-chlorothiazide level in all except 1. It was thought unlikely that chlorothiazide had any direct hypotensive action, since no change in blood pressure nor potentiation of ganglion blockade was observed after intravenous injection of large single doses. The sensitivity to pentolinium did not develop until the second day. This was not true with the non-quaternary ammonium compounds such as Mecamylamine and Pempidine. Since there was a slight shift of the urinary pH toward the alkaline side on first giving chlorothiazide, there was a resultant reduction in the renal excretion of these latter drugs, and therefore an increased hypotensive effect. The potentiating effect of chlorothiazide on pentolinium particularly affected the postural drop of blood pressure. Some postural hypotension was observed as a response to chlorothiazide itself in 4 of 13 patients. Three of these had a considerable fall in plasma volume while the fourth had an extensive sympathectomy previously. The postural response was abolished in each case by the infusion of sufficient Dextran to replace lost plasma volume.

SHEPS

# Gonadal Dysgenesis with Cor Pulmonale

*By* LINDSAY DAVIDSON, M.B., Ch.B., M.R.C.P., AND DONALD HEATH, M.D.

GONADAL dysgenesis is usually associated with multiple skeletal and visceral abnormalities as in Turner's syndrome. While most patients with this disease are normotensive, a few of the reported cases have had systemic hypertension,[1-3] which has been either idiopathic or a manifestation of an associated coarctation of the aorta. So far as we are aware, however, the association of gonodal dysgenesis with pulmonary hypertension has not yet been described. The following case report concerns a patient with Turner's syndrome who died with clinical signs resembling those of anoxic cor pulmonale with no evidence of preceding disease of the lung parenchyma.

## Case Report

As a small child the patient had winter bronchitis and attacks of pneumonia at the age of 3 and 6 years. Growth was normal to the age of 8 years but thereafter slowed and seemed to cease altogether at the age of 14 years. She was mentally subnormal. At the age of 14 years she had rheumatic fever and Perthe's disease. There was no evidence of menstruation by the age of 18 years and on this account a diagnosis of primary amenorrhea was made but treatment with Antuitrin S and G was without effect. At this time short stature, webbing of the neck, kyphosis, and hyperextensibility of the metacarpal joints were noted. The sella turcica and cervical spine were radiographically normal, and the heart and lungs were clinically normal.

At 26 years the patient was dyspneic on slight exertion but the respiratory system appeared to be clinically normal. Examination showed her to be a short, "thick-set" girl with Mongoloid eyes, her height being 55 inches (137 cm.) and her span 58½ inches (146 cm.). Webbing of the neck was prominent (fig. 1*a*). There was kyphoscoliosis of the dorsolumbar spine. She had a shield-shaped deformity of the sternum with a barrel-shaped chest (fig. 1*a*). Radiographic examination revealed diffuse vertebral osteoporosis, delayed closure of the iliac strip epiphyses, pelvic asymmetry, deformity of the right femoral head due to old osteochondritis, and a shallow right acetabulum. A wide cubital angle of about 17° was noted in both arms. The vaginal introitus was small and there was no development of the labia minora. All the secondary sex characteristics were very poorly developed. Axillary and pubic hair were scanty, the hair line was low, and there was no breast development (fig. 1*a*). Her cardiovascular system was found to be normal; in particular there was no evidence of coarctation of the aorta. The blood pressure was 130/80 mm. Hg and the radial pulse was regular at 72 per minute. The heart sounds were normal. The 24-hour urinary 17-ketosteroid excretion averaged 2.6 mg. daily, carbohydrate tolerance was at the lower limit of normal, and insulin sensitivity was normal. A diagnosis of Turner's syndrome was made and her photograph was used to illustrate the clinical features of this condition.[4] Treatment with 2 grains of thyroid extract per day and 2 mg. of hexoestrol 3 times a day were prescribed. When the basal metabolic rate rose to +55 per cent and the serum cholesterol had fallen to 80 mg. per cent, this therapy was discontinued.

She went to work as a clerk and at the age of 34 years was admitted to hospital again because of increasing breathlessness of 4 years' duration, so that she was capable of climbing only a short flight of stairs without stopping. She had experienced frequent attacks of bronchitis. She was always tired and felt cold, had gained weight, and had become slow in doing things. Since the age of 26 a marked malar flush and cyanosis had appeared. The radial pulse was normal in rate and character and the systemic blood pressure was 120/90 mm. Hg. There was slight lateral displacement of the cardiac apex. The first sound at the apex was reduplicated and the second sound in the pulmonary area was not accentuated. There were no cardiac murmurs and no signs of congestive cardiac failure. The chest was barrel-shaped and respiratory excursion was mainly vertical, the lateral expansion being only 1 inch. The vital capacity was 1,300 ml., this being 41 per cent of the predicted normal.[5] Her breathlessness was considered to be due to the low vital capacity. At this time kyphoscoliosis was again noted and was considered due to a developmental anomaly of the fifth lumbar vertebra. Radiographic examination of the chest confirmed the slight cardiomegaly and demonstrated enlargement of the hilar vessels with pulmonary congestion. The electrocardiogram showed incom-

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plete right bundle-branch block. The endocrine state was unchanged. Urinary gonadotrophins determined chemically gave values at the upper limit of the normal range (180 μg. per hour as glycine, 360 μg. per hour as glucose). The 17-ketosteroid excretion was 8 mg. in 24 hours.

Two years later she was seen in the out-patient department while recovering from an attack of bronchitis. There were no changes in the condition of her heart and lungs. Clinical examination suggested myxedema and she was given 2 grains of thyroid extract per day but this therapy was soon discontinued as her dyspnea grew worse.

Her final admission to the Queen Elizabeth Hospital at the age of 37 years was as an emergency for the urgent treatment of heart failure. Following a further attack of bronchitis she had rapidly developed extreme dyspnea and gross "swelling of the legs." Palpitation was troublesome. On examination she was severely cyanosed and orthopneic and was in congestive cardiac failure with gross ankle and sacral edema and a tender, enlarged liver. The signs of pulmonary hypertension dominated the clinical picture with a right ventricular heave, a diastolic shock, and a loud, reduplicated second sound in the pulmonic area. There were no cardiac murmurs but there was an apical protodiastolic gallop rhythm. She had a tachycardia of 120 per minute, the radial pulse being of poor volume. The cardiac impulse was impalpable. The systemic blood pressure was 115/80 mm. Hg. Chest expansion was very poor. There was hyperresonance to percussion in all areas. A teleradiogram showed enlargement of the heart with prominence of the pulmonary arteries. An electrocardiogram showed sinus rhythm with many ventricular extrasystoles and right ventricular preponderance. In spite of therapy for the heart failure with oxygen, aminophylline, mercurial diuretics, and penicillin, her condition deteriorated rapidly and she died 3 days later.

### Postmortem Report

The heart was enlarged. The right ventricle, stripped of fat, weighed 150 Gm., the normal weight being less than 65 Gm.;[6] the left ventricle weighed 122 Gm. Both the right atrium and ventricle were dilated and hypertrophied, the right myocardium being 9 mm. thick. The left cardiac chambers were normal; the left ventricle was 14 mm. thick. The aortic valve was bicuspid. It was thickened and scarred, the appearances being suggestive of healed endocarditis. The other cardiac valves were normal. There were dilatation of the pulmonary valve ring and atheromatosis of the pulmonary arteries. The origin, course, and distribution of the coronary arteries were normal; there was no coronary atheroma, myocardial fibrosis, or infarction. There were no congenital cardiac anomalies apart from the bicuspid aortic valve. There was superficial atheroma of the aorta, which was markedly hypoplastic but showed no evidence of coaretation. The inferior vena cava was double and contained no antemortem thrombus.

There were bilateral, serous, amber-colored pleural and pericardial effusions and dense left pleural adhesions. The trachea and bronchi were congested, and the mediastinal lymph nodes were enlarged. Both lungs were congested and edematous and the elastic pulmonary vessels were abnormally thick-walled and stood out prominently. The right lung (655 Gm.) was inflated with formalin to allow a detailed histologic examination and mensuration of the pulmonary vessels.

The liver and spleen were congested. There was mucosal cholesterolosis of the gallbladder, which contained a large, single cholesterol stone. The other abdominal viscera and the gastrointestinal canal were deeply congested. Both kidneys weighed 100 Gm. and were normal.

The endocrine glands showed no structural abnormalities. The weights were as follows: left adrenal 5.5 Gm.; right adrenal 6.0 Gm.; thyroid 15.5 Gm.; pituitary 1 Gm. The uterus and cervix were small and together weighed 10 Gm. A few Nabothian follicles were present. The Fallopian tubes were long and narrow, and the vagina was small. Small ridges were found in the expected sites for ovaries.

Histologically, the main pulmonary arteries and the small elastic pulmonary arteries within the lung parenchyma showed severe atherosclerosis (fig. 1*b*). The muscular pulmonary arteries (100 to 1,000 μ in external diameter) showed a definite but slight increase in medial thickness (fig. 1*c*). The pulmonary arterioles appeared normal apart from a slight cellular intimal proliferation in some of them. Intimal fibrosis was not seen in the pulmonary arteries and arterioles. Small spicules of bone were present in the lung parenchyma. There was no emphysema.

The gonadal remnants consisted of a small ridge of cellular fibrous tissue. The collagen fibers were arranged in parallel fasciculi at right angles to the peritoneal surface. Deep to this ridge were several tubules lined by low cuboidal epithelium and surrounded by smooth muscle and fibroblasts. No Leydig cells were seen (fig. 1*d*). Much lipoid was present in zona fasciculata of the adrenal

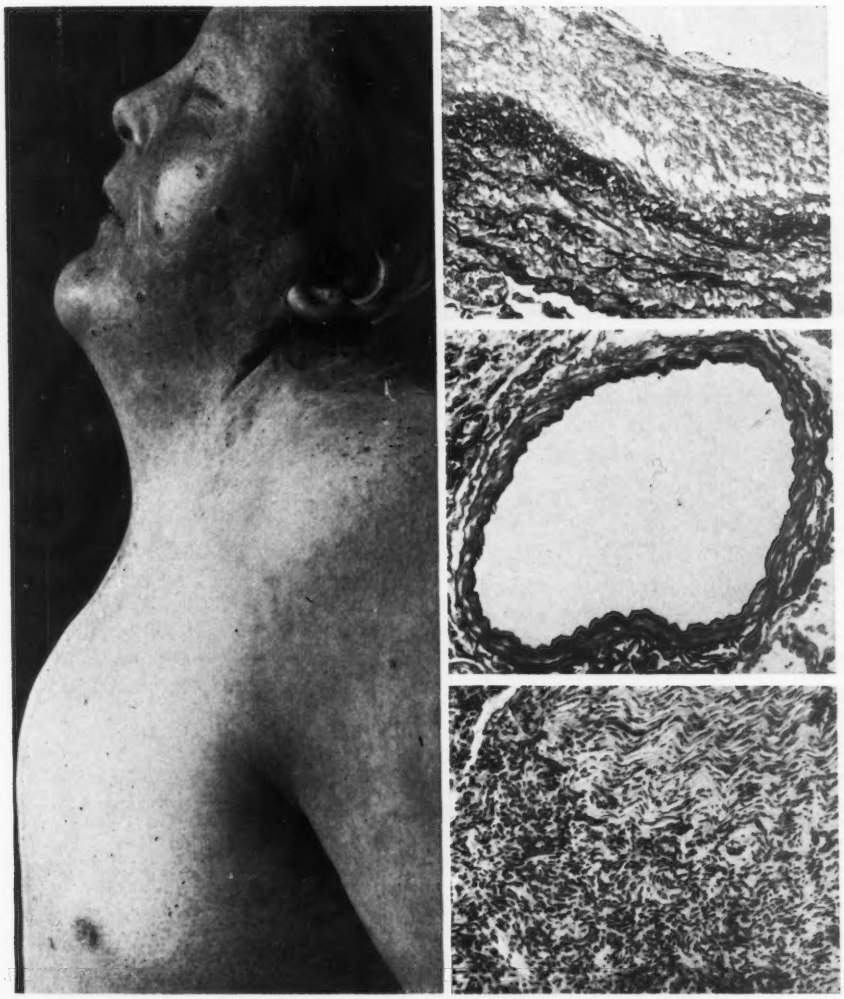

**Figure 1 a-d**

(a, left); (b, top right); (c, middle right); (d, bottom right).

*(a) A photograph of the patient showing the webbed neck, prominent "shield-shaped" sternum, and absence of breast development. (b) Part of a transverse section of a large, elastic pulmonary artery. Verhoeff's elastic and van Gieson × 100. (c) Transverse section of a muscular pulmonary artery showing the slight increase in thickness of the media characteristic of cases in which the pulmonary hypertension is due to pulmonary rather than cardiac disease. Verhoeff's elastic and van Gieson × 150. (d) Part of transverse section of gonadal ridge tissue showing the ovarian type stroma. Hematoxylin and eosin × 100.*

glands. The thyroid showed mild chronic nonspecific thyroiditis, with a heavy patchy lymphocytic exudate, and small acini lined by low-cuboidal epithelium and containing poorly stained colloid. The pancreas was normal. Sex chromatin was present in 25 per cent of all cells of the skin, but as only sections of paraffin-embedded material were available, the examination cannot be considered entirely satisfactory. The vaginal epithelium was atrophic, with occasional areas of desquamation, and there was a subepidermal chronic inflammatory exudate. The uterus was hypoplastic, with a vascular myometrium and a thick endometrium (nonsecretory and cystic). There were cystic dilatation of endocervical glands and a mild chronic cervicitis. The liver showed severe centrilobular venous congestion, with surrounding fatty change and the gallbladder showed cholesterolosis.

### Discussion

The basic data in this case are, clinically, that the patient died with symptoms and signs of pulmonary hypertension, and, pathologically, that there was right ventricular hypertrophy and dilatation with no evidence of a congenital cardiac anomaly capable of producing pulmonary hypertension or gross emphysema. The absence of marked medial hypertrophy and intimal fibrosis in the muscular pulmonary arteries (fig. 1*c*) makes a diagnosis of idiopathic pulmonary hypertension unlikely, for this latter disease is associated with severe structural changes in the pulmonary vasculature.[7] In fact the presence of only a slight increase in medial thickness in the pulmonary arteries to a value barely exceeding 5 per cent of the external diameter of the vessels is characteristic of pulmonary vascular changes associated with most cases of cor pulmonale due to primary lung disease.[7] This is probably due to the fact that the pulmonary artery blood pressure in these diseases is usually elevated only during the periods of congestive cardiac failure associated with respiratory infections.[8] Exceptionally, even in primary lung disease, the pulmonary vascular resistance may be chronically elevated to high levels and severe vascular changes would then be expected.[9]

We consider that this patient had anoxic cor pulmonale that developed as a result of the skeletal deformities of her chest, similar to the group of patients with kyphoscoliotic heart disease described by Hanley and his associates.[10] These workers have shown that patients with kyphoscoliosis may present with the clinical picture of anoxic cor pulmonale, the total lung capacity and vital capacity being reduced to as little as one quarter of normal. In the present case there was thoracic deformity with small lungs, emphysema was absent, and the vital capacity was only 1,300 ml. 4 years before death. In such a patient the vital capacity and ability to ventilate the lungs are adequate for resting requirements. The patient is unable, however, to increase alveolar ventilation sufficiently to meet the increasing oxygen needs of exercise or increased metabolism, with the consequent development of the clinical picture of cardiorespiratory failure so familiar in chronic primary pulmonary disease. When infection supervenes, pulmonary function may be inadequate to meet even resting requirements.

Hanley and his co-workers[10] demonstrated moderate pulmonary hypertension in 2 of their kyphoscoliotic patients who had recovered from heart failure. The pulmonary vessels of 2 of their patients who died did not show the histologic changes commonly associated with severe pulmonary hypertension, suggesting that permanent and severe elevation of pulmonary artery blood pressure is not essential for the development of congestive heart failure in such patients.

Clearly the clinical and pathologic features of our case are in complete conformity with the diagnosis of kyphoscoliotic heart disease secondary to the skeletal anomalies of the thorax. The repeated clinical finding of absence of accentuation of the pulmonary second sound until the final admission is explained by such a diagnosis. There appears to be no theoretical need to invoke an inherited congenital pulmonary hypertension in this case to explain the presence of cor pulmonale.

### The Sex Chromatin

In the present case there was evidence suggestive of chromatin negativity, which occurs in 85 per cent of cases of gonadal dysgenesis.[11] Previously accepted as a criterion of "maleness" it would now appear that nuclear sexing by this method is unreliable. Ford and his co-workers[12] have recently reported a patient with gonadal dysgenesis who was female anatomically and psychologically, whose cells were "male" as judged by nuclear sexing, and whose sex chromosomes were neither normally male nor normally female. As judged by the chromosomes there was no male component and half a female component, so that these workers concluded that there was no justification for considering this patient to be male in any sense. Chromosome studies were not carried out on the present case.

### The Gonadal Tissue

The histologic structure of the gonadal ridges in the present case is that of a fibrous ovarian-type stroma without differentiated ovarian elements and in association with small ducts lined by low-columnar epithelium (fig. 1*d*). Such appearances are very similar to those found by other workers,[13] although they reported additional features in some of their cases such as adrenal inclusions, Walthard's nests, and remains of Müllerian ducts.


## Summary

The clinical and pathologic features of a 37-year-old patient with Turner's syndrome are described. Dyspnea developed in the third decade and respiratory signs and symptoms finally dominated the clinical picture, so that the case appeared terminally as one of anoxic cor pumonale. The heart failure is considered to be related to the kyphoscoliosis present as one of the skeletal deformities of the syndrome.



## Acknowledgment

We gratefully acknowledge the permission of Professor Sir Arthur Thomson, Dr. S. L. Simpson, Dr. C. Hawkins, and Dr. A. Brian Taylor to report this case.



## Summario in Interlingua

Es describite le aspectos clinic e pathologic de un caso de syndrome de Turner in un patiente de 37 annos de etate. Dyspnea se disveloppava in le curso del tertie decennio, e signos e symptomas dominava finalmente le tableau clinic de maniera que le caso habeva terminalmente le apparentia de anoxic corde pulmonal. Es opinate que le disfallimento cardiac es relationate al cyphoscoliosis presente como un del deformitates skeletic in le syndrome mentionate.


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# SYMPOSIUM ON CONGESTIVE HEART FAILURE

## Pediatric Aspects of Congestive Heart Failure

*By* ALEXANDER S. NADAS, M.D., AND ANNA J. HAUCK, M.D.

IN MOST respects congestive failure is similar in all age groups, but some of the special features pertaining to infants and children are important. Detailed reviews on the subject have been published within recent years.[1-3]

One of the most significant differences between the congestive failure of adults and children is an etiologic one. Adults develop heart failure usually on a rheumatic, arteriosclerotic, or hypertensive basis. By contrast, congenital and rheumatic heart diseases are the principal etiologic groups in pediatrics; it is our impression that congenital heart disease leads more commonly to congestive failure than rheumatic heart disease, but no good statistical support of this view is available. Other less frequent etiologic entities in childhood are primary myocardial disease, paroxysmal supraventricular tachycardia, acute glomerulonephritis, anemia, and pericarditis.

We shall not discuss all these entities in detail but rather point briefly to some of their unusual features. We shall also discuss the clinical picture of congestive failure in children in general and make a few brief remarks about therapy and prognosis.

### Congenital Heart Disease

It is important to realize that the myocardium of children in congestive failure due to congenital heart disease is usually relatively healthy. Consequently, children represent a therapeutically more hopeful group in which successful surgical repair of the lesion may improve the circulation sufficiently to allow normal life expectancy.

The congenital cardiovascular abnormalities most commonly leading to congestive failure are in order of frequency, transposition of the great arteries, coarctation of the aorta, ventricular septal defect, aortic atresia, common atrioventricular canal, transposition of pulmonary veins, single ventricle, and patent ductus arteriosus.[1]

The age at onset of failure is noteworthy. Keith[1] stated that 90 per cent of the children who develop congestive failure do so within the first year of life. This may serve as a basis for optimism to parents of children who had no failure within this period of time.

Children with the syndrome of the tetralogy of Fallot seldom, if ever, develop congestive failure. The reasons are probably the relatively small pulmonary blood flow, the normal systemic flow, and the right ventricular pressure in the systemic range. We have so far encountered only 2 circumstances that led to the development of congestive failure in Fallot's tetralogy; namely, bacterial endocarditis and severe anemia. The latter may be a so-called "relative anemia" with hemoglobin values within the low normal range for children without arterial unsaturation.

Critical pulmonic stenosis with intact ventricular septum resulting in high right ventricular pressures sometimes twice the systemic level may, by contrast, lead to severe congestive failure early. The auscultatory findings of pulmonic stenosis without severe cyanosis, marked cardiac enlargement, and severe right ventricular hypertrophy by electrocardiogram may suggest this diagnosis. Emergency surgical intervention may be lifesaving.

Severe coarctation of the aorta may lead to congestive failure in early infancy. If failure with this malformation does not occur within the first 6 months of life, it rarely occurs before the second decade. Surgical treatment for

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alleviation of congestive failure should be employed only if vigorous medical management fails. Successful anticongestive measures may foster adequate growth and development and a return of the heart size toward normal. Relief of the aortic block then may be postponed to a later optimal time.

Among the groups of left-to-right shunts the ostium secundum atrial defects almost never lead to congestive failure in infancy and very rarely in childhood. By contrast some of the children with the severest congestive failure are those with an ostium primum septal defect. The addition of mitral and tricuspid regurgitation to the hemodynamic load of the atrial defect is probably the reason for this difference between the 2 types of atrial defects. Large ventricular defect with pulmonary arterial hypertension and a large pulmonary flow is also likely to lead to congestive failure early in infancy. Medical management usually, though not invariably, tides these infants over to an age when surgery can be performed with relatively low risk.

Patent ductus arteriosus is about the only left-to-right shunt leading to congestive failure that at the present time should be corrected surgically as soon as the diagnosis is made. Medical management should be utilized only as a preparation to operative intervention.

### Rheumatic Heart Disease

The appearance of congestive failure on a rheumatic basis is very rare under 2 years of age and probably assumes numerical significance only beyond 5 years. It has repeatedly been stated that rheumatic fever in the young is usually accompanied by maximal evidences of carditis. An additional axiom, the origin of which is hard to trace, is that a child with congestive failure on a rheumatic basis always has active carditis. One further point to be stressed is that children with congestive failure due to rheumatic heart disease always have a murmur; it may be stated with assurance that if no significant apical murmur is heard, the etiology of congestion must be other than rheumatic.

### Other Etiologic Entities

#### Arrhythmia

An analysis was made of the incidence of failure in children with arrhythmia. Cardiac decompensation was present in 22 of a group of 41 children, 29 of whom had supraventricular tachycardia,[4] 9 had atrial flutter, and 3 had ventricular tachycardia. Of those with failure, 75 per cent were 4 months old or less. Failure was not seen if the arrhythmia lasted less than 24 hours but was present in 19 per cent of those in whom it lasted 36 hours and in 50 per cent of those in whom it persisted for 48 hours. The heart rate, once it was above 180 per minute, seemed to have little influence on the development of failure; as many children with failure had heart rates from 180 to 240 as from 250 to 330.

Paroxysmal supraventricular tachycardia was almost always terminated successfully with digitalis. In the rare refractory case prostigmin was used with success.

#### Myocarditis

One of the most significant recent contributions in the field of heart disease of the young has been the isolation of Coxsackie virus group B from the hearts of infants succumbing from cardiac failure early in life.[5–8] The disease has appeared as early as 13 hours after birth and as late as 7 weeks of age. The illness has been characterized[9] by the onset of difficulty in feeding, fever, lethargy, and progressive cardiac failure. Less than half of the reported infants had symptoms of the central nervous system or hepatosplenomegaly. Twenty-one of the 27 patients have died.[9–11] The remaining 6 seem to have recovered completely.

Postmortem examinations revealed patchy necrosis and inflammation of the myocardium; the left ventricle was affected more than the right. Lesions have also been described in the brain, meninges, liver, spleen, adrenal and pituitary glands, pancreas, bone marrow, and striated muscle.[11]

In many cases a history of mild febrile illness, accompanied by headache or pleural pain has been elicited from the mother or

other members of the family. Coxsackie virus group B has been isolated on many occasions from these contacts of the infant. Intrauterine[9] as well as postnasal infection with this agent has been postulated and nursery epidemics have been reported.[5-7] The difference in susceptibility of the host to the virus is striking; the disease is mild in adults, but usually fatal in the newborn.

Two cases have also been reported of children with myocarditis and associated pericarditis. The virus was isolated from both patients who recovered.[10, 12]

Some of these babies have been treated with corticosteroids in addition to the usual anticongestive measures. The authors are not convinced of the superiority of this additional therapeutic effort.

In the majority of the myocarditides in childhood no etiologic agent can be identified, and they are termed idiopathic or Fiedler's myocarditis. There is little doubt that with the improvement of diagnostic technics specific etiologic agents will be identified. In the meantime all should be treated with vigorous, though cautious, anticongestive regimens.

Chronic extensive myocardial fibrosis, sometimes familial in occurrence, in other instances following an acute infection, often simulates the picture of constrictive pericarditis in children.

#### Acute Glomerulonephritis

In acute glomerulonephritis acute pulmonary edema is a rare complication but the onset may be sudden with rapid progression to a catastrophic climax. Quick and decisive action by the physician in face of such an emergency may prove to be lifesaving. Treatment should include oxygen, possibly under positive pressure, intravenous rapidly acting digitalis compound, aminophylline, morphine, and possibly tourniquets. Pulmonary edema may be the presenting symptom of acute glomerulonephritis with or without systemic arterial hypertension.

#### Anemia

Severe anemia may lead to congestive failure. Hemoglobin levels below 5 Gm. per 100 ml. of blood caused by leukemia, Mediterranean anemia, sickle-cell anemia, hypoplastic anemia, or even simple iron-deficiency state may cause severe cardiac failure even if the heart is structurally normal. Slightly higher levels (less than 7 Gm. per 100 ml.) may contribute to the development of congestive failure if the heart muscle is damaged by rheumatic carditis or nephritis or if structural deformities are present.

It is a good rule not to transfuse these children with whole blood but rather with increments of packed cells, slowly (5 to 10 ml. per pound every 8 to 12 hours). We have also tried in some infants with severe anemia to remove small aliquots of blood, replacing it with equal amounts of packed cells, thus avoiding an increase in circulating blood volume. The use of digitalis has not been particularly effective in the treatment of congestive failure secondary to anemia.

#### Pericarditis

Pericarditis as a cause of congestive failure is rare. Rheumatic pericardial involvement usually denotes severe pancarditis, and the accompanying failure is due to severe myocardial involvement. Constrictive pericarditis is very rare in the pediatric age group. Despite clinical and physiologic indications of this diagnosis, surgical exploration almost invariably reveals a normal pericardial sac. At autopsy, extensive myocardial fibrosis is usually found.

Acute purulent pericarditis, secondary to pneumonia or bacteremia, may cause pericardial tamponade and congestive failure. Rare instances of so-called acute "benign" pericarditis or severe rheumatoid arthritis also may lead to cardiac tamponade. Finally, in the postoperative period after cardiotomy, hemopericardium may represent a serious surgical emergency.

Pericardial tamponade causing severe right-sided failure is particularly difficult to identify in infants whose short necks do not allow adequate evaluation of the jugular venous pulse. The discovery of marked cardiac enlargement and muffled heart sounds without murmurs, coupled with a high index of suspicion in the conditions mentioned, may lead

to the consideration of pericardial effusion in the differential diagnosis. Careful search for the presence of pulsus paradoxus of over 10 mm. of mercury, low systolic and narrow pulse pressure, clear lung fields, and electrocardiographic changes of pericarditis may lead to the correct diagnosis. Pericardial tap or pericardial exploration under local anesthesia, if necessary, is the procedure of choice if the diagnosis is seriously suspected. We wish to stress the inadequacy of radiologic and even fluoroscopic attempts to distinguish between a maximally dilated heart and accumulation of fluid in the pericardial sac.

Once the diagnosis of cardiac tamponade is made, surgical evacuation of the compressing fluid is the treatment of choice. If the fluid is purulent, vigorous treatment with antibiotics is indicated. Digitalis usually is not helpful, although we cannot attest to its being harmful. Diuretics may be indicated.

### Clinical Manifestations of Congestive Failure

The clinical picture of congestive failure differs to a certain extent in children from that commonly observed in adults. Purely left-sided failure with paroxysmal nocturnal dyspnea, rales at the bases, frothy blood-tinged sputum, and the "butterfly" distribution of pulmonary edema on the radiogram is practically unknown in children. Contrariwise, the clinical profile of right-sided failure with facial edema, hepatomegaly, and jugular venous distention is the common picture. Periorbital edema was so marked in a 20-month-old girl with atrial tachycardia of 1 month's duration that she was sent to the hospital with the diagnosis of nephrosis. Other manifestations of right-sided failure, such as dependent edema and ascites, are found less often in children than in adults. Anorexia, irritability, excessive perspiration, and restless sleep are common to both left- and right-sided failure.

Although the dominant feature of heart failure in the pediatric age group is systemic congestion, most of the patients indeed represent combined right- and left-sided failure, with the former dominating the picture. Although the evidences of systemic congestion are obvious, left-sided failure may be suspected only by observing tachypnea in a patient without cyanosis. Heart failure in even purely left-sided lesions (patent ductus arteriosus, coarctation of the aorta) is often recognized first on the basis of peripheral edema and hepatomegaly; the primary left ventricular failure is manifested only by the more subtle sign of tachypnea. Sometimes mothers note rapid respiration before the appearance of systemic congestion. This is often not recognized by physicians as an indication of left-sided failure.

**Table 1**

*Dosage of Oral Digoxin*

| | 0 to 2 years | 2 to 13 years |
|---|---|---|
| Total digitalizing dose given in 3 divided doses | 0.03 to 0.04 mg./lb. | 0.02 to 0.03 mg./lb. |
| Daily maintenance dose given in 2 divided doses | 1/4 to 1/3 digitalizing dose | 1/4 to 1/3 digitalizing dose |

Purely right-sided failure is seen in relatively few instances: in pure pulmonic stenosis, in pulmonary vascular obstruction, in complete transposition of the pulmonary veins, and occasionally in atrial defect. Purely left-sided failure is seen rarely in some infants with a large patent ductus, severe coarctation of the aorta, endocardial fibroelastosis, or mitral valve obstruction.

### Therapy of Congestive Failure

The therapy of congestive failure in a child differs little from that in an adult. The general medical principles used in treating adults also apply to infants and children.

Any one of several preparations of digitalis can be used in pediatrics with benefit. A suggested dosage schedule for Digoxin is given in table 1. The principle of individualizing digitalis dosage to achieve maximal therapeutic or minimal toxic effect cannot be overemphasized. Unusual sensitivity to digitalis may be present in some patients with myocarditis, so that in them digitalization should be accomplished cautiously under close observation.

Diuretic agents are safe as well as effective

**Table 2**

*Dosage of Mercurial Diuretic Agents*

| Age | Minimum dose | Maximum dose |
|---|---|---|
| 0 to 1 month | 0.1 ml. | 0.25 ml. |
| 1 month to 2 years | 0.2 ml. | 0.5 ml. |
| 2 years to 13 years | 0.3 ml. | 1.0 to 1.5 ml. |

**Table 3**

*Guide to Dosage of Chlorothiazide (Approximate Values)*

| Age | Dose |
|---|---|
| 0 to 2 years | 125 mg. b.i.d. |
| 2 to 13 years | 250 mg. b.i.d. to t.i.d. |

in the young. Tables 2 and 3 list approximate dosages according to age. The intravenous administration of aminophylline one half hour after a mercurial injection also is useful in children who do not respond adequately to mercurials and digitalis alone. Considerations regarding electrolytes and diuretics in the pediatric age group and in adults are similar.

A low-sodium diet should be given only if it can be made palatable enough for the child. Children need an adequate protein intake for growth. Consequently, if the only way a qualitatively and quantitatively adequate diet will be consumed is by offering foods with normal sodium content, we would choose to do so if more diuretics have to be given in order to maintain an edema-free state. If, on the other hand, a low-sodium diet is tolerated and the need for diuretics can be reduced or abolished, this course would seem preferable.

The physical comfort of the child and relief of restlessness and anxiety are extremely important. Morphine has proved to be an invaluable drug in this regard. Doses of 0.05 to 0.075 mg. per pound are usually satisfactory. Similar doses are also sufficient for the treatment of acute pulmonary edema. A device that we have found useful for propping young babies in an upright position is illustrated in figure 1. If desired, it can be converted easily

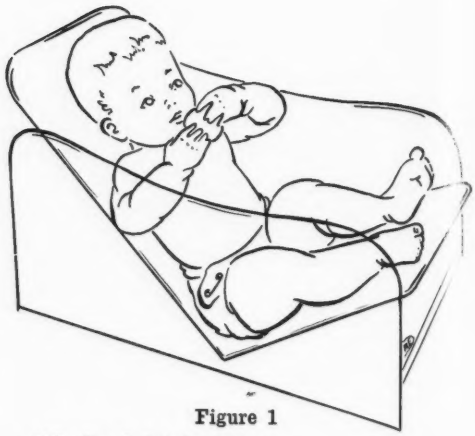

**Figure 1**

"Cardiac bed" for infants.

from a seat to a flat surface so that the infant may be examined in the supine position. An oxygen tent may be used if it does not frighten the child and is kept cool, but it should quickly be abandoned if the baby is afraid of it.

Since many infants with rales have pneumonia as well as congestion of the lungs, antibiotics are probably indicated if there is any sign of infection or if the child is debilitated. In the latter case fever and leukocytosis may be absent in the presence of pneumonia.

## Summary

Congestive failure in infancy and childhood may occur in a number of diseases. Congenital heart disease, however, is probably the most common cause of failure, with rheumatic fever second. Although the basic physiology of cardiac decompensation is similar in adults and children, the presenting clinical picture may be somewhat different in the 2 groups.

We believe that infants and children with congestive failure should be treated vigorously, for we have the distinct impression that the mortality rate of these youngsters with severe heart disease has decreased appreciably since a more optimistic attitude prevails among parents and doctors about these problems. Vigorous use of anticongestive measures and antibiotics is worthwhile and results in many instances in the survival of an infant

to an age when successful surgical repair is feasible. Certainly not all babies with congestive failure due to congenital, rheumatic, or other kind of heart disease can be salvaged. But surely the experience of the last few years has given us a much more optimistic outlook on this entire field. There are enough children attending school and enjoying life today who seemed at "death's door" in infancy to make us hesitate to give an unqualifiedly poor prognosis to almost any child in congestive failure. Similarly, we are more and more reluctant to suggest cardiac surgery as a dramatic emergency measure except in a few well-chosen cases. Intelligent medical management can salvage a large number of these children and allow them to survive to an age when relatively low surgical mortality may be offered.


### Summario in Interlingua

Congestive disfallimento cardiac pote occurrer durante le infantia e pueritia in association con un numero de morbos. Tamen, congenite morbo cardiac es probabilemente le causa le plus commun de disfallimento, con febre rheumatic occupante le secunde rango. Ben que le physiologia fundamental de discompensation cardiac es simile in adultos e juveniles, le aspectos clinic de presentation pote differer in un certe maniera in le 2 gruppos.

Nos opina que infantes e juveniles con disfallimento congestive debe esser tractate vigorosemente, proque nos ha distinctemente le impression que le mortalitate in iste gruppo de patientes pediatric con sever morbo cardiac ha decrescite appreciabilemente depost que un attitude plus optimista predomina del parte de parentes e medicos con respecto a iste problemas. Le uso vigorose de mesuras anticongestive e de antibiotics vale le pena e resulta in multe casos in le superviventia de un infante usque al etate ubi le reparo chirurgic pote esser effectuate a ben successo. Certo, il non es possibile salvar omne le infantes con disfallimento congestive resultante de morbos cardiac congenite, rheumatic, o altere. Sed nonobstante il es un facto que le experientias del passate annos justifica un prognose multo plus optimista in iste campo integre. A iste tempore un sufficientemente grande numero de juveniles visita le scholas e gaudi del vita ben que illes se trovava "in mano de morte" in lor infantia pro non permitter a nos le formulation de un uniformemente sombre prognose pro omne infante in disfallimento congestive. Similemente, nos es de plus in plus reluctante de recommendar chirurgia cardiac como heroic mesura de urgentia excepte in rar e ben seligite casos. Un intelligente programma medical pote salvar un grande proportion de iste infantes e render possibile lor supervivientia usque a un etate quando un relativemente basse mortalitate pote esser offerite.


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# Congestive Phenomena Occurring in Pregnant Women with Heart Disease

*By* C. Sidney Burwell, M.D., and James Metcalfe, M.D.

PREGNANT women with heart disease may exhibit the signs of either pulmonary or peripheral congestion. Evidences of venous congestion in the lower extremities, including the development of pitting edema, are not unusual during pregnancy in normal women and should not be taken as evidence of danger, even in the cardiac patient, without supporting data. In pregnant women with heart disease significant congestive phenomena occur most often in association with mitral stenosis. In this situation they are due to the *obstruction* at the mitral valve that leads to congestion and edema of the lungs. In a smaller number of pregnant women with heart disease congestive phenomena are due to *myocardial failure*, and in this case the congestion may affect either the pulmonary or the peripheral circulation according to whether left or right ventricular failure is present. Since, in well over half our pregnant cardiac patients, the major hemodynamic problem is mitral stenosis, significant congestive phenomena during pregnancy are observed most frequently in the lungs.

The left ventricular failure that rarely occurs in pregnant women with heart disease is most often associated with aortic valve disease and only rarely with hypertension. Ventricular failure may also occur in association with specific disease of the cardiac muscle. The most common cause is acute rheumatic myocarditis. It has also been observed in other varieties of myocardial disease including myocardial infarction.

Whatever the predominant *cardiac* lesion in congestive failure may be, such failure is intensified or indeed precipitated by a long list of extracardiac factors, including certain specific physiologic changes of pregnancy.

### Physiology of the Maternal Circulation During Pregnancy

The changes in the maternal cardiovascular system during pregnancy are complex and incompletely understood, but 3 of them, the increases in heart rate, cardiac output, and blood volume lead directly to vascular congestion. These 3 changes are closely related, at least in time; all reach their highest level, not at term, but from 6 to 10 weeks before delivery, and then decline significantly until labor ensues. At their peak values, the resting pulse rate averages 10 beats per minute above the nonpregnant value, the resting cardiac output is increased by about 40 per cent, and the blood volume is elevated by about 30 per cent of control values. It should be remembered, however, that this statement of general performance indicates only the average behavior of a large number of pregnant women with and without heart disease; in the individual patient variations in the intensity and in the time of maximal change undoubtedly occur. The mechanism by which these changes may lead to disability and occasionally to death in pregnant women with heart disease is best understood if mitral stenosis is taken as an example.

### Physiology of Mitral Stenosis

The basic defect hemodynamically in mitral stenosis is an obstruction to the flow of blood from left atrium to left ventricle. The maintenance of a normal volume of blood flow

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through the narrow valve orifice requires an increase of pressure in the left atrium, and a pressure rise of similar magnitude in the pulmonary veins and pulmonary capillaries. An *increase* in cardiac output in such circumstances necessitates a further rise in left atrial, pulmonary venous, and pulmonary capillary pressures. Effective blood flow through the mitral valve occurs only during diastole; the increase in heart rate that accompanies pregnancy cuts down the diastolic time for flow through the mitral valve, so that a further increase in left atrial, pulmonary venous, and pulmonary capillary pressure is necessary to maintain cardiac output. The increase in total blood volume that accompanies pregnancy is apparently shared between the pulmonary and peripheral vascular circuits. This increase in pulmonary blood volume distends the pulmonary vascular system and, in patients with significant mitral stenosis, leads to still greater increases in pressure in the capillaries. When the pressure in these vessels exceeds approximately 30 mm. of mercury, it leads to transudation of fluid; if pulmonary capillary hypertension persists, the transudation causes pulmonary edema. The woman with mitral stenosis, then, is in increased danger of developing pulmonary edema during pregnancy. Such pulmonary edema is due to mechanical obstruction to blood flow and is different in mechanism from the pulmonary congestion secondary to left ventricular myocardial failure. The distinction between these 2 varieties of pulmonary congestion should be kept in mind in planning the therapeutic approach in a given patient.

### Prevention of Venous Congestion

The principle of managing mitral stenosis during pregnancy is to adopt ways and means that limit or restrict the cardiac output, the total blood volume, and the cardiac rate. The total cardiac burden of the pregnant woman includes not only pregnancy but a great variety of other burdens. The physician must be concerned with the algebraic sum of those factors that influence the output of the heart, the rate of the heart, or the volume of blood in the vascular tree. He must think constantly of the *total* cardiac load resulting from the patient's *total* situation, including pregnancy.

In most pregnant women with heart disease, congestive phenomena can be prevented by a program of management that applies these principles to the individual patient. The objective of management is not necessarily to keep the total cardiac load at a minimum. What is needed is to keep the total load safely within the tolerance of the individual patient.

In constructing such a program of management we must consider factors that have 3 essential characteristics. First, they are not necessary to the continuation or success of the pregnancy; second, they impose a cardiac burden; third, they can be limited or eliminated. Important individual factors in patients' lives that lead to an increase in heart rate, in cardiac output, or in blood volume include the following: (1) physical activity, (2) emotional stress, (3) ectopic rhythms with tachycardia, (4) anemia, (5) obesity, (6) infections, (7) hyperthyroidism, (8) factors that influence the blood volume, such as infusions, transfusions, and increased intake of sodium. Some of these factors are more frequently operative during pregnancy than in the nonpregnant woman. For instance, iron deficiency may manifest itself for the first time as anemia during pregnancy. Infections of the upper respiratory tract or the genitourinary tract are common in pregnant women. The hypertensive toxemias of pregnancy sometimes add to the total burden in women with heart disease; control of the hypertensive disorders of pregnancy by sodium restriction has been an important factor in lowering the maternal mortality in women with heart disease. So has the virtual elimination of puerperal sepsis.

Attention must also be given to prevention of 2 specific diseases, acute rheumatic fever and subacute bacterial endocarditis. In our opinion prophylaxis against rheumatic fever is advisable in all patients with rheumatic heart disease during and for an indefinite period after pregnancy. The customary pro-

phylaxis against bacterial endocarditis is also employed during and for 3 days after labor.

### Management of Venous Congestion*

"In a rare patient from the prenatal medical clinic and an occasional patient first seen late in pregnancy, symptoms and signs of venous congestion have developed. Peripheral edema, while disturbing in its prognostic implications, is seldom dangerous. Pulmonary congestion and pulmonary edema carry danger of immediate death and therefore demand prompt and organized treatment."

#### Hospitalization and Rest

"Every patient with pulmonary congestion observed in the clinic is admitted to the hospital with the objective of immediate rest. We believe this is achieved by allowing the patient to pick her own best resting position until pulmonary edema has cleared. This is often in an easy chair. A bed is made more comfortable by placing its 'head' legs on four- to eight-inch blocks, so that the entire frame is tilted. Elevation of the head of the bed and flexion of the patient's knees allow comfortable maintenance of the sitting position. Elastic stockings are applied to above the knee to combat thrombo-embolic disease. The use of a bedpan is usually more tiring than the use of a bedside commode or travel to the toilet by wheelchair."

#### Sedation

"Increased mental and physical rest is the aim of sedative therapy. In our experience morphine in small, repeated doses has no equal for this purpose. An initial dose of 10 mgm. is given intramuscularly, followed at four-hour intervals by equal or smaller doses, as indicated."

#### Sodium Restriction and Diuresis

"The increased blood volume of pregnancy is one of the identifiable factors in distention of the pulmonary vascular tree. If pulmonary congestion appears, sodium restriction to about 200 mgm. daily is usually effective even if a similar program at home has not prevented the development of pulmonary congestion. In such a diet, salt-free milk and bread are used. Dialyzed low-sodium milk is now available. It is palatable and relatively inexpensive."

In patients who accept and follow rigid sodium restriction, diuretic agents are seldom necessary in our experience. In patients exhibiting important venous congestion despite sodium restriction, diuretic agents are employed. Before entering upon a program of forceful or prolonged diuretic attempts, the physician must evaluate the importance of venous congestion in his patient. Edema of the legs, unaccompanied by other evidence of venous hypertension, is less dangerous and disabling than strenuous diuretic medication. When a program of diuresis is decided upon, our current practice is to begin with 500 mg. of chlorothiazide twice daily for 3 days of each week, judging our success by changes in fasting body weight measured daily, and evaluating the serum electrolytes each week before diuretic therapy is reinstituted. When such a program does not result in satisfactory improvement and weight loss, intramuscular mercurial diuretics are tried. The possibility of electrolyte depletion by these measures should be kept constantly in mind.

#### Methods of Decreasing Venous Return to the Heart

"The venous return can also be diminished, at least transiently, by the application of tourniquets to the extremities or by phlebotomy. These measures are frequently helpful in the acute emergency of pulmonary edema. The level of blood hemoglobin should be checked before phlebotomy, but we have resorted to this measure in emergency situations in anemic patients knowing, in some cases, that transfusion would subsequently be necessary.

"When tourniquets are used to obstruct venous return they may initially be placed on all four extremities if they are not so tightly applied that arterial obstruction results. At half-hour intervals *one* is removed and re-

*Some of the following paragraphs are extracted *in toto* from the book, *Heart Disease and Pregnancy, Physiology and Management*, by the authors.[1] These extractions are indicated by quotation marks.

placed after one half-hour, at which time another is removed, rotating the obstruction in an orderly serial fashion. Sudden removal of several tourniquets would result in a sudden large increase in venous return which might be dangerous."

**Methods of Slowing the Heart Rate**

"In patients with mitral stenosis, tachycardia is dangerous since it decreases the time available for diastolic flow through the mitral valve. When atrial fibrillation or paroxysmal atrial tachycardia is present, digitalis is the drug of choice in controlling heart rate. In the presence of normal sinus rhythm this drug is frequently disappointing in producing a decrease in heart rate. Indeed, no adequate method of decreasing the heart rate in sinus tachycardia exists. Serpasil is currently being tried for this purpose in our patients. If the tachycardia is accentuated by anemia, thyrotoxicosis, or blood-loss, measures designed to combat these are indicated."

**Digitalis**

"Pulmonary congestion is not always due to myocardial failure. Indeed, myocardial failure is an unusual cause of pulmonary congestion in our patients; the common cause is an obstruction to blood flow through a stenotic mitral valve with pulmonary vascular hypertension secondary to the mechanical impediment. In such a situation the chief therapeutic result of digitalis is to slow the heart rate.

"When pulmonary congestion or edema develops in patients with aortic valve disease, then digitalis is indicated. We have, in general, sought to anticipate ventricular failure in such patients, using oral doses of digitalis foli (0.1 Gm. three times daily for five days, then 0.1 Gm. daily) at the earliest suspicion of myocardial failure.

"In the presence of pulmonary edema, rapid digitalization is employed, even in patients we judge to have predominant mitral stenosis. We have used digoxin for this purpose, beginning with 0.5 mgm. intramuscularly, repeating this dose at four-hour intervals for a total initial dose of 1.5 mgm. over a 12-hour period. We do not use this glycoside for maintenance therapy but shift to digitalis leaf."

**Oxygen**

"The use of oxygen in the treatment of pulmonary edema has many advocates. It certainly appears to be indicated if it causes symptomatic relief, and is probably indicated when it can be tolerated without apprehension. Unfortunately it frequently does cause apprehension and restlessness, and in such situations its continuance must be decided upon in the light of the individual case. In general, an oxygen 'tent' is tolerated more readily than oxygen administered through a nasal tube, while the face mask is badly received by most patients."

**Other Measures**

"The administration of aminophylline in the management of pulmonary edema is indicated for several reasons. It is a bronchodilator, and many believe that bronchoconstriction frequently occurs in conjunction with pulmonary edema. It has the additional advantage of its properties as a xanthine diuretic, and Goodman and Gilman[2] ascribe *direct myocardial stimulation* to the xanthines. Usually 0.25 Gm. is given slowly intravenously."

**Prevention of Recurrences**

"Following recovery from an acute episode of pulmonary edema, the patient's activity, sodium intake, sleeping position and total program of living must be rescheduled, to avoid recurrences. In pregnant patients strict modification may be necessary only for the duration of pregnancy, but plans for future medical care, including consideration of mitral valvotomy, should be carefully laid for patients who have experienced pulmonary edema.

"The importance of sodium restriction has already been emphasized. Our experience indicates that the diet actually consumed often differs from that recommended. Therefore patients on restricted sodium intake should be seen weekly.

"In our clinic all patients are encouraged

to report *at once* if symptoms develop or increase. When a cardiac patient misses an appointment we have learned to be concerned. Such patients may fail to turn up because they are in need of additional medical help."

### Cardiac Surgery During Pregnancy

Despite rigid limitation of the total burden on the patient's heart, an occasional woman is unable to tolerate the cardiac expenditures of pregnancy. If this is judged to be the case in a given patient and if surgical measures are applicable, these should be employed before pregnancy is undertaken. Emergency cardiac surgery during pregnancy has not been found necessary in our experience to date, but we may sometime see a patient, early in pregnancy, in whom evidence of pulmonary congestion persists, despite rigid restrictions accurately followed. In such a patient we would prefer interruption of pregnancy rather than cardiac surgery as the first step toward cardiac rehabilitation. This is sometimes unacceptable for social or religious reasons, and therefore cardiac surgery may rarely be indicated even during pregnancy. It is imperative to make the necessary judgments before persistent congestive failure forces the hand of the surgeon.

The cardiac burdens of pregnancy exhibit certain known variations. The cardiac output, the total blood volume, and the heart rate all reach a maximum 6 to 10 weeks before term. Many patients experience an improvement in symptoms as the point of maximum load is passed and they come into the period of less severe load which precedes delivery. Hamilton and Thomson[3] showed that the incidence of congestive phenomena in pregnant women with heart disease was highest from the thirtieth to the thirty-fourth week, which corresponds to the time of the maximum hemodynamic load of pregnancy.

### Labor and Postpartum Period

Most patients who have gone through pregnancy without exhibiting congestive phenomena or whose congestive symptoms have been controlled by appropriate therapy are able to go through labor and delivery without intensification of congestive failure. It may be pointed out that the work of labor is discontinuous and that periods of increased work and increased oxygen need are separated by periods of relative rest. It should be emphasized again that the work of the heart in terms of cardiac output is significantly smaller at term than it was 6 to 10 weeks previously, and therefore at the time of delivery a pregnant woman with heart disease has an amount of cardiac reserve which she did not have a month before. It has been found by experience to be important that women with heart disease come up to the time of delivery and labor in optimum condition. Skillfully organized and executed delivery is a vital matter and here, while continued close cooperation is essential, the obstetrician plays the decisive role. The presence of heart disease is not an indication for cesarean section but if a good obstetrical indication for abdominal delivery exists, there is no experience that would warrant the denial of such a procedure to a woman with heart disease.

Congestive phenomena are occasionally intensified or may even develop for the first time during the postpartum period. During this period an intricate series of profound readjustments is being made in the maternal physiology. Some of these adjustments are the reestablishment of normal water and electrolyte balance, a new equilibrium among the hormones and the tissues that produce them, and appropriate changes in the blood volume and in the total capacity of the vascular system. Too little is known about the physiology of the postpartum period to make a didactic or arbitrary application to the management of heart disease. It must be remembered that heart failure can get worse or develop during this period and that the heart disease which has required management during pregnancy still requires management after delivery. Moreover, the patient herself is in a more complex situation and has additional family responsibilities. These matters should all be taken into account in planning

the postpartum program of a cardiac patient. If congestive phenomena occur during this period, they should be managed by the accepted methods.

In larger scope, pregnancy is an episode in the life of the patient with heart disease—an important episode accompanied by increased danger, but self-limited in duration and generally successfully tolerated. As our understanding of the physiology of pregnancy and the physiology of heart disease has increased the safety of pregnancy in the cardiac patient, other aspects of pregnancy have become increasingly important. One aspect which should concern us here is the importance of pregnancy in bringing women under medical supervision. About 50 per cent of our patients with heart disease were unaware of its existence before pregnancy. Even under our high standards of living and patient care, a surprising number of women have their first contact (since their own birth) with a physician when they consult him for obstetrical help. This has 2 important implications. First, the obstetrician must have a high level of suspicion with regard to heart disease and should develop an effective working relationship with an internist for final diagnosis and help in effective management. Second, the obstetrician and his medical consultant should accept as part of their responsibility the orientation of the patient, not only through the hazards of pregnancy, but through the years that follow. In this sense, pregnancy represents an opportunity for the physician to develop a long-term plan for these young women that will postpone, and sometimes prevent, the development of congestive phenomena in the years ahead.

> Keep thy heart with all diligence;
> for out of it are the issues of life.[4]

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# Unusual Causes of Heart Failure

*By* HOWARD B. BURCHELL, M.D., PH.D.

A DISCOURSE on unusual causes of heart *failure* naturally follows and overlaps any discussion on unusual causes of heart *disease,* and some repetition is unavoidable. However, one outstanding distinction is that in which the normal heart fails on exposure to a gross overload, as for example after the production of a large aortic-caval fistula such as has followed operation for an intervertebral disk.[1, 2]

In any discussion on heart failure, some definition of the subject is mandatory. The term "heart failure" in this communication indicates a physical disability with a propensity for dyspnea, edema, and fatigability wherein the heart plays a dominant role, albeit perhaps not always as the central figure on the disease stage but, if not, as the director-producer in the wings.

In addition to the traditional two types of heart failure, namely the one in which the dominant feature is edema and overt venous congestion, and the other in which it is episodic pulmonary edema (frequently the two are combined), one must recognize two other clinical types. The first of these is exemplified by the ambulatory patient whose main symptom is marked fatigue, and the second, by the bed patient who presents the picture of pallor, apprehension, weakness, and perhaps a sense of breathlessness without change in respiratory effort. In the first category may be observed many patients having severe mitral insufficiency, and in the second, patients with advanced myocarditis; in the latter particularly, a hypotonic, hyponatremic syndrome may be associated.

In the approach to unusual causes of heart failure, two worth-while classifications are given in tables 1 and 2. The traditional academic classification of disease into congenital and acquired varieties remains a basic approach, worth the effort of recall from student days (table 1). At another time, a parallel approach with focus sequentially on extrinsic and intrinsic causes may open doors leading to the recognition of previously occult causes of the failure (table 2). In many instances in which one may be puzzled by the nature of the heart failure, one may be rewarded by looking at a distance from the heart, because practically any organ system may be the chief malefactor and have both initial and continued responsibility in the various heart failure syndromes. In listing possible contributing causes (table 3), one cannot restrict with ease the conditions to rarities; rather, one can claim only that the causes are sufficiently unusual that they are not encountered regularly in day-to-day practice. It is only by constant vigilance that one will be alert to recognize the unusual and explore the possible etiologic ramifications. In recognizing the unusual, one may occasionally reap the reward of identifying a causal factor that permits of complete cure.

### Congenital Causes of Failure

In the neonatal period, the child with heart failure may be suffering from one defect or a combination of many defects. Clues will be forthcoming from the auscultatory findings and the electrocardiogram, the size and shape of the heart, and the pulmonary vascularity in the presence or absence of cyanosis.

Out of the host of possibilities, one needs to mention specifically the rarity of total anomalous pulmonary venous connection, with obstruction to outflow either because of a single stenotic vein or a stenotic foramen ovale. Tricuspid atresia with a stenotic foramen ovale, premature closure of the foramen ovale, stenoses of the pulmonary veins, con-

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**Table 1**

*Traditional Academic Classification of Causes of Heart Failure*

| |
|---|
| Congenital causes |
| 1. Neonatal, late postnatal |
| 2. Gross structural, myocardial |
| Acquired causes |
| 1. Traumatic (valve cusp) |
| 2. Chemical or toxic (emetine or endocrine therapy, alcohol?) |
| 3. Inflammatory (infections, hypersensitivity states, granulomatous lesions) |
| 4. Degenerative (nutritional, presbycardia) |
| 5. Neoplastic (intracavity, myocardial, pericardial) |

**Table 2**

*Classification of Heart Failure from the Standpoint of Extrinsic and Intrinsic Causes*

| |
|---|
| A. Extrinsic cause, heart basically normal |
| 1. Effect by dynamic overload |
| 2. Effect by myocardial injury |
| B. Intrinsic cause |
| 1. Gross mechanical (hydraulic) defect |
| a. Valvular deficiencies, large shunts |
| 2. Gross myocardial deficiency |
| a. Cause indeterminate, for example, familial idiopathic hypertrophy |
| b. Cause determinate, for example, hemochromatosis, gargoylism |
| C. Combinations |

genital pulmonary valvular insufficiency, and cor triatriatum are examples of lesions resulting in the picture of heart failure wherein specific reconstructive procedures may be considered. Other defects leading to heart failure in the infant are patent ductus arteriosus, coaretation of the aorta, severe pulmonary stenosis, and large ventricular septal defects.

Not a rare but still an uncommon cause of heart failure in young infants is paroxysmal tachycardia, which is, or should be, readily recognized. Also, in the infant age, one must be alert to the possibility of an anomalous coronary artery arising from the pulmonary artery; in some patients, the recognizable syndrome of episodic anginal distress and characteristic electrocardiographic pattern may occur, while in others, manifestations of heart failure with cardiac enlargement may be outstanding.

In both infancy and later years, the condition of endocardial sclerosis (or fibroelastosis) may present a diagnostic challenge. However, with knowledge concerning the various syndromes associated with this condition and knowledge concerning both the dilated and the constricted form of the ventricle (the clinical picture of constrictive pericarditis often being mimicked), one may be reasonably certain of one's diagnosis. One form of heart disease that may, I believe, be placed in a category of endocardial sclerosis is the form wherein the right ventricle is primarily involved and the picture of pure right heart failure makes its appearance.[3] Ebstein's disease, though rare, should be remembered as a possible cause of heart failure in a young child. Here, the characteristic auscultatory, electrocardiographic, and roentgenologic findings should make the diagnosis readily apparent. In some instances, however, the right ventricle, being fairly competent, may result in a left-to-right shunt at the atrial level and produce a confusing picture.

A rare cause of heart failure, which may become clinically manifest in late childhood or early adulthood even though the defect is primarily congenital, is so-called corrected transposition of the great vessels, with insufficiency of the left atrioventricular ("mitral") valve. One should know enough about the condition to be alerted to it when one encounters a young individual having mitral insufficiency, evidence of left ventricular hypertrophy, left atrial enlargement, and perhaps second- or third-degree heart block without a history of rheumatic fever. Another type of late failure related to a primary congenital defect is that occurring consequent to rupture of an aortic-sinus aneurysm, with its superficial simulation of a patent ductus arteriosus.

It may be emphasized here that occasionally subaortic stenosis occurs in association with pulmonary stenosis, with the ventricular septum being intact and the pulmonary stenosis dominating the picture and with the electrocardiogram suggesting primarily the pulmo-

**Table 3**

*Some Contributing Causes of Heart Failure by Organ Systems*

| Organ system | Etiologic factor | Mechanism |
|---|---|---|
| Central nervous system | Ischemic brain disease | Hypertensive crises |
| | Paraplegia | Hypertensive crises |
| Thyroid | Hyperthyroidism | Increased output, tachycardia, decreased efficiency (?) |
| | Myxedema | Inadequate output, pericardial effusion |
| Adrenal | Hypercorticism | Sodium retention with water, hypertension |
| | Medullary tumor | Hypertension, hypertensive crises |
| Kidney | Unilateral or bilateral ischemia | Hypertension |
| | Acute nephritis | Hypertension, hyperemia |
| | Arteriovenous fistula, kidney | Hypertension-increased cardiac output |
| Liver | Hepatitis | Increased output, retention of fluid |
| | Cirrhosis | Increased output, venoarterial shunt; x factor-nutrition (?) |
| Uterus | Pregnancy | Increased output, effect like arteriovenous fistula |
| | Postpartum state | Pulmonary embolism, unknown factors |
| | Fibroids ? | ? |
| Gastrointestinal tract | Malabsorptive syndromes | Nutritional deficiencies |
| Bone | Myeloma | Amyloid anemia |
| | Paget's disease | Effect of arteriovenous fistula |
| Lung | Vascular disease; pulmonary emboli, Bilharzia | Cor pulmonale |

nary obstruction. As the pulmonary stenosis may need surgical correction under direct vision, the prime necessity is for the surgeon to be cognizant of the fact that there may be an occult aortic lesion in such a rare case and to be prepared to correct it in addition to the more overt pulmonary obstruction.

In addition to the gross structural defects of congenital origin, there are myocardial functional aberrations such as defects of a biochemical nature, some of which are not as yet understood or identified. In gargoylism, an inborn error of metabolism produces deposits in the muscle cell, and heart failure occurs. In some families, sudden deaths have occurred in the siblings with few findings apart from slight enlargement of the heart. The routine methods of examination have not revealed the cause. In one such family under my observation, a girl showed a markedly prolonged Q-T interval in the electrocardiogram as the only evidence of abnormality, and the cause of this has remained completely obscure.

### Acquired Causes of Failure

In this, the second category of heart disease, the usual subgroups of traumatic, chemical or toxic, inflammatory, degenerative, and neoplastic causes are briefly reviewed.

#### Traumatic Causes

Traumatic lesions of the heart with survival of the patient, but with heart failure, are rare. The most commonly observed are the penetrative lesions, with failure of the circulation related to acute tamponade. The possibility of such a problem occurring in an investigative laboratory from cardiac puncture deserves mention. My colleagues and I have seen one patient with traumatic rupture of the ventricular septum related to nonpenetrating trauma present with the picture of heart failure. Surgical repair having been accomplished, the heart has been returned to a normal functional state. I have not observed rupture of the aortic valve, but instances of rupture of the chordae tendineae of the mitral valve have been diagnosed, some of these occurring without known previous disease or identified trauma. A history of rather sudden appearance of dyspnea and a loud murmur, and the development of rapidly progressive heart failure, should orient one's thoughts toward this diagnosis.

**Chemical or Toxic Causes**

A prime example of chemical, or toxic, lesions is that of emetine therapy, which, however, rarely causes gross heart failure. One might also consider in this subcategory excess endocrine therapy, as may occur with large doses of adrenal steroids or with overdoses of thyroid hormones.

**Inflammatory Causes**

In the subcategory of inflammatory causes are the subdivisions: (1) direct infections, (2) hypersensitivity state including possible autoimmune disease, and (3) granulomatous lesions. It is important to emphasize that the diagnosis of myocarditis, which, excluding rheumatic lesions, was frowned upon 2 decades ago, is now recognized as a not infrequent clinical entity, for example as a complication of viral diseases such as poliomyelitis, influenza,[4] and the Coxsackie[5] group of infections. These viral agents may be responsible for the initiation of heart failure "de novo" in some instances, but more frequently if valvular disease is already present. In the hypersensitivity group, certain patients with disseminated lupus present evidence of myocardial disease. Also in some cases of lupus, pulmonary vascular disease may develop and cor pulmonale may make its appearance. In the granulomatous group, in addition to types of idiopathic myocarditis, well-documented cases of sarcoid with gross myocardial involvement[6] and heart failure have been reported. This syndrome has not been observed personally.

In recent years, there has been an apparent increased incidence of patients who have a relentlessly progressive type of chronic myocarditis, with the total duration of life after onset being some months or years. The clinical picture is often characterized by severe disturbances in rhythm and conduction, with heart block and paroxysms of ventricular tachycardia being characteristic. Late in the disease, the patient often has a persistent presystolic gallop rhythm and presents a shocklike picture already mentioned in the introduction as typical of some patients with heart failure and a low cardiac output. The clinical picture is essentially akin to that seen on occasion in years past, namely the picture wherein there has been a severe toxic myocarditis in diphtheria. Perhaps as an example, par excellence, of heart failure that is rare and is caused by myocarditis due to a specific agent is the failure related to *Trypanosoma cruzi* (Chagas' disease). Extensive personal experiences with myocarditis of varying types and causes have been recorded by Mattingly[7] and Brigden.[8]

A cause of heart failure that previously was uncommon but now is encountered with increased frequency is healed subacute endocarditis, the patient usually presenting with symptoms and signs of heart failure related to either gross aortic or mitral insufficiency. When both aortic and mitral insufficiency are present, it may be rewarding to consider the possibility that the aortic insufficiency was primary and the mitral incompetence secondary. This mitral incompetence may not be related to the usual location of destructive vegetations involving the contiguous portions of the mitral valve, or to rupture of the chordae tendineae, but rather due to a ruptured mycotic aneurysm of the anterior (or aortic) leaflet of the mitral valve. If one were fortunate enough to have perforations of both aortic and anterior mitral cusps, surgical cure of both the aortic and the mitral insufficiency is possible. Rupture of an aortic-sinus aneurysm simulating a patent ductus arteriosus has been mentioned, and at this time one may mention having seen 2 cases of syphilitic aortic aneurysm with rupture into the superior vena cava in one case and into the pulmonary artery in the other case; a continuous murmur and heart failure were present in both cases.

The syndrome of constrictive pericarditis in its characteristic form should be readily recognized, but when it is associated with a large cardiac shadow, a chronic effusion and a constricted epicardium, it is not easily differentiated from conditions of enlarged heart or other causes with chronic heart failure,

such as amyloid disease and endocardial sclerosis with a dilated left ventricle. Pericardial disease can persist for many years, producing the picture of chronic heart failure, and when it occurs in older people one may be lulled into a false sense of security by a previous diagnosis of hypertensive and coronary atherosclerotic heart disease. In some instances, one's suspicion of pericardial disease may properly lead to further investigation, utilizing such technics as cardiac catheterization, angiocardiography, or even direct surgical exploration. In regard to the preceding problem, tuberculosis as an etiologic possibility should never be forgotten, and this is true irrespective of the age of the patient. Rarer causes of chronic heart failure with pericarditis are chronic hemorrhagic effusions, slowly progressive metastatic malignancy, and cholesterol pericarditis.

**"Degenerative" Causes of Failure**

The term "degenerative heart disease" is justifiably in bad repute, but one can borrow it from the traditional subcategories of acquired disease and attempt to justify its use by defining the term as indicating a deleterious change in the function of the myocardium related to defects in its nutrition and in the functional integrity of its individual units. Among the nutritional inadequacies, one may place beriberi heart disease, which was reported on recently by Jones.[9] Earlier studies indicated that a high-output type of failure was to be uniformly expected, but this has not proved true of all cases.

Occasionally, patients in the older age group with heart failure are encountered and one may be at one's wit's end to assign a logical etiologic diagnosis. While there has been a tendency, in large part related to statistical chance, to attribute the heart failure to hypertension in past years, or to coronary insufficiency, there may not be sufficient clinical evidence of such an etiologic background to be satisfying to an inquiring mind. To such a phenomenon, the term "presbycardia"[10] has been applied, but one may consider this term only as a convenience, and it is difficult from my experience in cardiologic practice to define it and call it an established entity.

The possibility that some patients with heart failure have defects of the myocardium or the pericardium consequent to ionizing radiation cannot be ignored, but as a cause of failure such defects must be rare. In the general category of "degenerative" lesions may also be grouped the patients who are given the diagnosis of idiopathic hypertrophy, and these patients may or may not have some degree of endocardial sclerosis. One should exercise great caution in making the diagnosis of endocardial fibrosis in adult patients, even when these may present with a stereotyped syndrome including the features of chest pain of an anginal type, progressively severe heart failure, and systemic emboli. It is uncertain in such adult patients whether the endocardial fibrosis is or is not the primary lesion, and one may be properly dissatisfied with this term as a clearly defined etiologic diagnosis. Reports of endocardial sclerosis as it occurs endemically in the native African[11] have engaged the attention of clinician and pathologist alike, but so far it is not clear whether or not the disease has an etiologic relationship to that seen in this country. Other types of apparently nutritional myopathies in the African also apparently occur.

To be mentioned also in the category of degenerative myopathies are those instances in which heart failure develops post partum, giving rise to the concept of "postpartum heart disease." I have not observed a pure instance of idiopathic postpartum heart failure, and one careful review[12] has indicated that there are usually adequate reasons why the situation might have occurred, these reasons being related to specific types of heart disease or hypertension existing prior to childbirth. In this general area, however, must be mentioned the frequency with which idiopathic pulmonary hypertension has its onset in the immediate postpartum period. This naturally suggests that pulmonary emboli, that is, minute thrombi or amniotic fluid from the uterine cavity, has initiated the pul-

monary arteriolar lesion. It is evident that another explanation must be forthcoming for other women not having such an onset and for men with this condition. The course of patients with idiopathic pulmonary hypertension usually runs from progressive effort disability to intractable right heart failure in a few years.

#### Neoplastic Causes

The traditional last subcategory in a classification of acquired disease is that of neoplastic lesions. Here one may think of primary and secondary neoplasms in the thorax and their location within the cardiac cavities, in the myocardium and in the pericardial space. The cases of atrial tumor have reached sufficient numbers that one cannot regard this as a particularly rare lesion, and one always hopes, if an individual presents with the picture of right inflow stasis or of mitral valve obstruction, to run into clues that may lead to the establishment of such a diagnosis and eventual surgical care.

In rare instances a tumor may invade the right atrium through the inferior vena cava and produce the picture of heart failure. Tumors of the kidney are the usual offenders in this regard. Primary tumors of the myocardium are rare, but may occur in infancy as rhabdomyosarcoma, with heart failure the presenting symptom. Secondary tumors of the myocardium, even though extensive in some instances, rarely lead to heart failure, and I have no example of such a case. Both primary and secondary tumors involving the pericardium are not really rare, and they produce not only the picture of acute tamponade, but also the picture of chronic heart failure of the congestive type. Of interest is the possibility that a mesothelioma occurring within the pericardium might present as a pericardial effusion, mild fever, and recurring arthralgias, simulating rheumatic fever on cursory introduction.

### Contributing Causes of Heart Failure

Many of the contributing causes of heart failure mentioned in table 3 are not truly rare. Practically all organ systems are listed. Although conditions of the skin, reticuloendothelial system, fat depots, and gonads are not included, this does not signify that they have no importance for heart disease. Despite the fact that skin diseases are not responsible for heart failure, they may provide diagnostic clues such as café-au-lait spots, "spiders" and other hemangiomas, or more specifically, scleroderma or angiokeratoma corporis diffusum universale. In patients who have hypertensive crises, one usually thinks of pheochromocytoma; this condition presents a dramatic situation when a patient is admitted as an emergency to a hospital and the blood pressure is found to be in the neighborhood of 300 mm. of mercury systolic and 200 diastolic, and pulmonary edema is present. That such a state is sometimes related to transient ischemia of the brain may not be readily appreciated, but the presence of such a syndrome has been proved repeatedly in our clinic.

In hypertensive disease and heart failure associated with an arteriovenous fistula in the hilus of the kidney,[13] there is an unusual wedding of 2 etiologic factors of failure, namely the hypertension and the high cardiac output. The mechanism of the high output as related to the fistula is self-evident, but the hypertension as it could be attributed to ischemia of the kidney distal to the fistula is of greater novelty.

In respect to Paget's disease of bone, the evidence that there may be an arteriovenous type of connection in the involved bones is clear-cut, and in patients with extensive disease there may be a high cardiac output. My colleagues and I have observed the phenomenon of a high cardiac output as originally described by Edholm and associates,[14] but as yet we have no instances of heart failure that can be primarily related to Paget's disease.

### Comment

In this review, a number of different approaches to classification of unusual causes of heart failure have been outlined, and a listing of unusual and perhaps not so unusual contributing causes by the various organ systems

has been given. By definition, the unusual has been considered that which is of infrequent occurrence in day-to-day cardiologic practice, including that which often is unrecognized because of its uncommon and occult nature in the clinic but which, as later revealed at postmortem examination, often may not be so unusual. One has been tempted to reapply a previously discussed alphabetic or encyclopedic approach[2, 15] to the problem of heart failure, but it would seem better to identify the features of the failure and to follow ramifications of the specific clues to the various congenital or acquired conditions along the avenues of thought that are most promising. Herein, in regard to the congenital area, only a few interesting conditions have been listed, without any pretense to completeness or discussion of differential diagnosis.

Reference to unusual cardiac conditions may be had in the book published by Reich,[16] the size of which also indicates the magnitude of the problem and the difficulty of differentiating the unusual from the usual. In the particular category of chronic myocarditis, additional emphasis is needed, as this condition appears to be becoming more common, the nature of the process is not understood and multiple etiologic agents may be operative. Along with Mattingly,[7] I should like to stress the importance of cardiac arrhythmias and conduction defects in patients with chronic myocarditis. It may be mentioned that following the report[17] that toxoplasmosis might be a cause of chronic myocarditis, the serum of our patients has been tested to indicate whether this infection might have been present, but the results have been negative.

### General Conclusions

In the whole province of the discussion of the uncommon, there may be the aura of immodesty, pomposity, and sophistry. To be meaningful and have pragmatic values, a communication concerning the unusual should lead to better understanding of disease and to its control or cure. To have mentioned premature obliteration of the foramen ovale, with hydrops fetalis, which results in such early death, has no value for the practitioner, yet the condition has real significance in the attempt to understand a congested circulation and the mechanism of endocardial sclerosis. On the other hand, mention of cor triatriatum has practical value, as the thought of its possible presence might lead to the establishment of its presence and its surgical cure.

One is overwhelmed with the multitude of rarities that may be encountered, and there is a geographic distortion of what constitutes a rarity; for instance, endocardial sclerosis remains a rarity in this country, but is stated to be one of the most common causes of heart failure in Uganda among the native Africans. Likewise Chagas' disease has not been recognized as having been seen at the Mayo Clinic, yet I am told[18] that in Brazil it is a common cause of heart failure; the medical student readily diagnoses it and suspects the disease on such slight evidence as right bundle block. In the approach to the unusual, one should avoid not only a geographic provincialism in diagnosis, in regard to colloquial labels, but also a "time provincialism," meaning the avoidance of parroting of diagnostic labels fashionable at the time.

There is no pretense to completeness in this personal appraisal of the problem, and only a few articles, a minute fraction of the available literature, which have especially piqued my interest are given as references.

The mass of data pertaining to rarities with which the medical scholar is confronted is so formidable that he may well fail in the solving of an assigned problem. The analogy, now fashionable, to a computer seems an apt one: the usual mind cannot integrate the findings, remember all the possibilities, make the necessary discriminatory matching of each sign and symptom with all the cases of each rarity in the world literature; in other words, both his biologic computer and the programming of it seem inadequate. Indubitably, there will be a place for electronic computers in the diagnosis of the unusual in the future.

A medical rarity may serve as a true test

of a physician, as measured by his answer to a question: when he is confronted with a difficult problem in his specialty and has overlooked or disregarded signs that suggest a rare condition susceptible of specific therapy and cure and that have been thought to be diagnostic by another consultant, can he affirm, "I hope that my colleague is right and that the patient's life will be saved, rather than that he is wrong and that my reputation will be saved"? (A tinge of hope for saving of the reputation is admittedly justifiable.)


### Summario in Interlingua

Es presentate un revista de causas inusual de disfallimento cardiac. Le termino "disfallimento cardiac" es definite como designante un stato de invaliditate physic con un propensitate pro dyspnea, edema, e fatigabilitate in que le corde ha un rolo, si non central, al minus dominante.

Es discutite le valor complementari de duo classificationes del causas inusual de disfallimento cardiac. Le un distingue causas congenite ab causas acquirite, durante que le altere establi gruppos distincte de causas intrinsec e extrinsec. Le duo classificationes es presentate in Tabulas 1 e 2, supplementate in Tabula 3 per un lista de causas contributori.

Le autor organisa su detaliate discussion del causas inusual de disfallimento cardiac in le gruppos de causas congenite e acquirite, con un subdivision del secunde in causas traumatic, chimic e toxic, inflammatori, degenerative, e neoplastic.


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# Rehabilitation in Congestive Heart Failure

*By* HOWARD A. RUSK, M.D., AND MENARD M. GERTLER, M.D.

THE philosophical concept of rehabilitation has gained wide recognition over the past 10 years. One of the reasons for the rapid advance in this comparatively new discipline is that numerous studies have begun to define scientifically the meaning and practice of rehabilitation.[1, 2] The scientific knowledge thus attained in concepts of rehabilitation coupled with the increased physiologic and biochemical knowledge of congestive heart failure and a better understanding of the meaning of cardiac functional classification in terms of ergometry and ergonomics has at long last permitted a more scientific as well as clinical basis for rehabilitation.[3, 4]

The projected population in the United States in 1980 is estimated to be about 200,000,000. There appears to be no doubt that by 1980, 45 per cent of the individuals in this population will be over the age of 45. Accordingly, nearly 90,000,000 individuals will be in an age group where cardiac disease will be the most prevalent. At the present time, the cost of heart disease to the nation in terms of merely dollars and cents exceeds 4 billion dollars annually. This does not include, of course, the intangible loss in happiness, comfort, and equanimity to the individual and his family. It is therefore imperative to recognize the present as well as the future needs for rehabilitation of the patient with cardiac disease.

The technics and practice of rehabilitation procedures have proved to be of inestimable value in the hemiplegic patient,[5, 6] and the patient with coronary heart disease.[7-9] Results in various industries prove conclusively that patients with coronary heart disease not only resume their original occupation but continue their duties with less absentee days and with at least as much efficiency as do the healthy, noncardiac group.[10] In addition it has been demonstrated in a group of industrial cardiac patients in functional classes I and II that over 70 per cent returned to their former occupations and maintained an equal work status with their noncardiac colleagues.[10]

Rehabilitation of the patient with congestive heart failure involves the same team approach, cooperation, and principles established in other areas of rehabilitation. Specifically, for the patient with cardiac heart failure the physician either alone or in cooperation with the other disciplines must endeavor to obtain the maximal cardiac function with minimal risk to the individual patient so that he can perform his role with the most efficiency and acceptability in the environment in which he lives and works.

Eventually all cardiac patients, whether hypertensive, arteriosclerotic, rheumatic, or congenital, are more likely to develop the syndrome of congestive heart failure than any other complication.[11] The exact number of individuals who are hospitalized or who are ambulatory with congestive heart failure is unknown, for the statistics on this problem are unsatisfactory and have not been considered in great detail. For diverse reasons, it is difficult to know at the present time the exact incidence of congestive heart failure. A survey of a hospital ward and a survey of 1,000 consecutive private patients indicated (a) 31 cases of grades 3 to 4 congestive failure in 180 ward beds and (b) 93 private cases with grades 1 to 2 congestive failure. (No attempt was made to classify the etiologic type of heart disease.)[12]

### Congestive Heart Failure as Related to Rehabilitation

The syndrome of congestive heart failure may be looked upon in simple terms as a bodily state wherein there is a failure of bio-

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chemical energy within cardiac muscle to be converted into mechanical energy for propulsion of blood to meet the requirements of various organs. Accordingly, there are 3 areas in which failure may develop: (a) failure in energy production or substrate availability, (b) failure in energy transportation, and (c) failure in energy utilization.[13, 14] According to this enlightened and biochemical concept of congestive heart failure, the correction of failure is basically the correction of bioenergetics in the areas described. The heart must be placed in a condition in which it meets its demands easily. This is the first basic principle of cardiac rehabilitation, i.e., know the exact diagnosis and evaluate the treatment from the viewpoint of the whole patient. There are 5 other basic principles of cardiac rehabilitation:[15]

1. Evaluate the patient's medical, psychologic, social, and vocational status.
2. Individualize management, including diet, drugs, physical activity, emotional stress, environmental stress, etc.
3. Discuss with the patient the nature of his disease and the prognosis and treatment, as well as the assessment of his capacities and how he can best arrange his life to fit his needs.
4. Make every effort to eliminate the patient's fear of heart disease.
5. Encourage the patient to live the best life possible within the limits (if any) imposed by his disease.

Energy measurements of cardiac work have been calculated directly and indirectly. The direct measurement exceeds the indirect by far in accuracy but cannot be employed routinely or continually. These measurements consist of bioenergetic studies of mitochondrial systems prepared from animals in experimental heart failure[15] and coronary sinus catheterization.[16] The indirect measurements are not without criticism but are practical and useful for the evaluation of the patient for cardiac rehabilitation. The methods employed most frequently for the evaluation of energy costs of myocardial work are based upon *indirect* calculation from oxygen consumption of the total individual during a standard sustained exercise, dye-dilution studies, and ballistocardiogram.[17, 18] The results obtained by Kottke,[2] Bruce,[18] Jones,[19] Benton and Rusk,[20] and Hellerstein and Ford[21] have contributed much to our knowledge concerning the functional capacity of the heart during and following illness. This information coupled with the classic information of Passmore and Durnin[4] on the energy cost of various human endeavors has placed cardiac rehabilitation on a human, scientific, and practical basis.

### Special Rehabilitation Procedures

One of the most important phases in the rehabilitation of patients with congestive heart failure is a proper diagnosis both as to functional and therapeutic classification. With the proper diagnosis, specific medical treatment for the particular type and degree of heart disease may be instituted. In addition to the general supportive and therapeutic measures given to the patient with congestive heart failure such as digitalis, low-sodium diet, diuretics, and vitamins, specific measures for (a) coronary disease may include anticoagulants and an isocaloric diet low in short-chain fatty acids, (b) for hypertensive cardiovascular disease the use of one or more of the many antihypertensive drugs, and (c) in rheumatic heart disease, the use of salicylates and steroids during the early phase of failure may be mandatory. In addition prevention of further rheumatic episodes is in order with the use of antibiotics.

A further word may be said in favor of calculated exercise in coronary heart disease. Exercise has been shown recently to be effective as a protection against coronary heart disease in 3 areas: (1) it increases collateral circulation in the myocardium;[22] (2) it increases the plasmin serum levels thus aiding in the dissolution of blood clots;[23] (3) it decreases the incidence of atherosclerosis in rabbits fed high-cholesterol diets.[24] The exercise should not be sustained but rather intermittent with an output of not more than 4.0 calories per minute.

Jones[19] has classified cardiac patients with

**Table 1**

*The Interrelationships Between Cardiac Functional Classification, Physiologic Symptoms, and Ergometrics*

| Cardiac functional classification | Physiologic symptoms | Maximum calories per minute sustained | Maximum calories per minute intermittent |
|---|---|---|---|
| I. | Patients with a cardiac disorder without limitation of physical activity. Ordinary physical activity causes no discomfort | 5.0 | 6.6 |
| II. | Patients with a cardiac disorder with slight to moderate limitation of physical activity. Ordinary physical activity causes discomfort | 2.5 | 4.0 |
| III. | Patients with a cardiac disorder with moderate to great limitation of physical activity. Less than ordinary physical activity causes discomfort | 2.0 | 2.7 |
| IV. | Patients with a cardiac disorder unable to carry on any physical activity without discomfort | 1.5 | |

*Modified from Jones.[19]

congestive failure into the functional classification of the American Heart Association and determined the output in terms of calories per minute. These are summarized in table 1. It is very important in assaying the performance of work for the cardiac subject to note the effect of peak sustained effort in comparison with intermittent effort, because the same amount of caloric output may be accomplished by a cardiac subject working intermittently over a longer period without danger while at peak sustained effort the work may be done in a shorter period but the cost could be devastating, e.g., in coronary heart disease.[19]

### Choice of Occupation

The choice of occupation may require more than just a casual glance at occupations and ergometrics. There are, in addition, intangible factors which are very specific for each individual and the type of cardiac disorder. An individual, for example, who has had a myocardial infarction should not be permitted to engage in an occupation which may endanger the lives of the public, i.e., bus driver, train engineer, or pilot.

**Table 2**

*Energy Costs of Various Activities and Occupations*[4]

| Activity | Cal./min | Activity | Cal./min |
|---|---|---|---|
| Washing & dressing | 2.6 | Inspector | 1.2 |
| Washing face & combing hair | 2.5 | Printer | 2.0 |
| Sitting | 1.6 | Shoe repairing | 3.6 |
| Standing | 2.0 | Shoveling | 10.6 |
| Sewing, 30 stitches/min. | 1.1 | Postman | 10.0 |
| Peeling potatoes | 2.4 | Planing hardwood | 9.1 |
| Polishing floor | 4.5 | Grass cutting | 4.3 |
| Bed making | 5.4 | Gardening | 4.4-5.6 |
| Beating and brushing carpets | 7.8 | Hoeing | 4.1 |
| Climbing stairs | 6.0-10.0 | Driving a car | 2.8 |
| Walking 3.0 m.p.h. | 5.6 | Golfing | 5.0 |
| Typing | 1.5 | Tennis | 7.1 |
| | | Cycling | 5.0-10.0 |
| | | Dancing | 5.2 |

The ergometric and ergonomic studies of Passmore and Durnin and others have permitted the removal of the guess work from a physician's instructions to patients. Instead of saying to a bed ridden patient, "Do a little more" the patient may be told to shave in bed (1.0 cal./min.); sit up in bed for an hour (3.0 cal./min.); walk down the hall for 15 minutes (4.0 cal./min.). Thus, by giving specific instructions, the patients progress may be gaged, e.g., if symptoms of angina or dyspnea or signs of tachycardia or increased venous pressure do not appear with low cal./min. activities, then activities of increased cal./min. are instituted until patient is completely ambulatory and self sufficient according to the scheme of activities of daily living.[25] A few of these activities are summarized in table 2.

### Conclusions

In addition to the necessity for meticulous diagnosis, physical evaluation, and prescription the psychologic and emotional factors are of primary importance. Confidence based on gradually increased work experience and a

close patient-physician relationship are fundamental in establishing the milieu necessary for successful rehabilitation. As Spiller has so aptly said, "Action absorbs anxiety." In congestive heart disease, action is an invaluable therapeutic tool but like all potent remedies, it requires all of the skills of the dedicated clinician to prescribe it safely and effectively.


### Summario in Interlingua

A parte le necessitate del plus meticulose attention in diagnose, evalutation physic, e prescription, factores psychologic e emotional es de importantia primari in le rehabilitation de patientes con congestive disfallimento cardiac. Confidentia basate super un gradualmente augmentate carga de labor e un intime relation inter le patiente e le medico es de importantia fundamental in establir le milieu que es necessari pro successo in le rehabilitation. Como Spiller lo ha si ben exprimite: "Action absorbe anxietate." In casos de congestive morbo cardiac, action es de inestimabile valor therapeutic, sed—como omne potente remedios—pro esser salve e efficace, illo debe esser prescribite con omne le habilitate de un dedicate clinico.


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# CLINICAL PROGRESS

## Heart Disease and Filtrable Viruses

*By* JOHN M. PEARCE, M.D.

THE concept embodied in this discussion of heart diseases caused by filtrable viruses is based on experiments done on rabbits in my laboratory during the past several years. It has been possible to show that when filtrable viruses are introduced into the animal body by a peripheral route they can specifically infect the heart and there produce anatomic alterations and functional derangement; that this ability is not the property of a single virus but is common to several; and finally that an important factor in inducing the cardiac localization of the virus is a decrease in the amount of oxygen supplied to the heart. Clinical and postmortem experience indicates that under somewhat similar conditions viral myocarditis and endocarditis occur in human beings as well.

As is the case so often, the first production of viral heart disease came as an unintended byproduct of another experiment. In a study of virus-III disease in rabbits, animals were inoculated intratesticularly for routine passage of the agent. For the sole purpose of procuring normal serum, these same animals were bled by cardiac puncture immediately before inoculation. Because of our constant interest in heart disease, and of our desire to have a large background knowledge of normal cardiac anatomy, these hearts were examined microscopically after the animals were sacrificed 4 to 6 days later. Almost all had extensive myocarditis, while many had in addition pericarditis and endocarditis. In these inflammatory lesions the intranuclear inclusion bodies characteristic of virus-III disease were easily recognized. This observation, coupled with the fact that punctured hearts of animals that had not been inoculated with a virus were never the seat of inflammation, was convincing evidence that the virus was not only present in the lesion, but was indeed the cause of it. In addition there has never been any difficulty in recovering virus from the heart.

The introduction of the needle into the heart seemed to be the factor causing the virus that presumably was circulating in the blood stream to localize in the heart and there to produce the characteristic inflammation. Since it has long been known that vaccinia virus injected intravenously will produce a localized lesion in scarified areas of skin, it is not surprising that the grossly traumatic procedure of sticking a needle into and through the pericardium, myocardium, and endocardium would also cause a blood-borne virus to gain a foothold and produce lesions in these structures. A search for a method of causing cardiac localization of peripherally introduced virus that would be more physiologic and would more closely simulate conditions that might occur in the natural life and environment of the animal led first to the use of an intravenous solution of gum acacia and then to intravenous beta hypophamine (Pitressin). The first of these intravenously injected solutions would increase the "load" on the heart by augmenting the volume and viscosity of the circulating fluid, and the second would achieve the same effect by elevating the blood pressure and constricting the coronary arteries. Clark and Svec[1] had been able

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to produce bacterial endocarditis by preceding the infecting dose of bacteria by a large intravenous injection of gum acacia, and Nedzel had had similar success with beta hypophamine in causing the localization of bacteria in the heart valves of dogs.

Of the 3 methods of bringing about cardiac localization of the virus and hence carditis, the most frequently successful was the injection into the marginal ear vein of the rabbit of 50 ml. of a 20 per cent solution of sterile gum acacia in 0.85 per cent sodium chloride as rapidly as could be done. Ninety per cent of the rabbits so treated developed one or more variations of cardiac lesions, while only 50 per cent of the Pitressin-treated animals had viral inflammatory lesions in the heart.

Pericarditis is the least common lesion, but when it does occur it is quite striking (fig. 1). The exudate and the reaction in the pericardium closely resemble those seen in the pericarditis accompanying rheumatic fever in human beings. The entire heart is covered by a coating of dull, sticky fibrin that is most abundant at the base, in the crevices around the atria, and between these structures and the ventricles, and in the interventricular grooves. Under the microscope it is apparent that this is almost pure fibrinous pericarditis. There are no polymorphonuclear leukocytes, and the leukocytes that are present are chiefly mononuclear cells that have slightly basophilic cytoplasm and frequently suggest desquamated and proliferating mesothelial cells of the epicardium. Almost always there is some organization, and usually a rich growth of fibroblasts extends into the fibrin from the heart wall. Inclusion bodies can be found both in the cells enmeshed in the fibrinous exudate and in the new connective tissue at its base. As might be expected, pericarditis occurred in those hearts that were most severely affected in other respects and not uncommonly extensive areas of myocarditis lay immediately adjacent to the inflamed epicardium.

Lesions of the endocardium, both mural and valvular, are somewhat more frequently

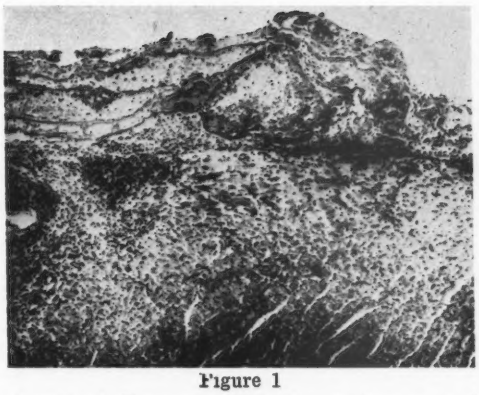

**Figure 1**

*A coat of fibrin containing few leukocytes, and these mostly lymphocytes, overlying the epicardium of a virus III-infected heart that was the seat of myocarditis as well. Hematoxylin and eosin stain.*

encountered than are those of the pericardium. For instance, in one early series of experiments 13 of 17 affected animals developed lesions of the mural endocardium, and in 7 of these 13 one or more of the valves was also inflamed. The affected valve was thickened by an infiltration of mononuclear cells, by a proliferation of fibroblasts among which mitotic figures were numerous, and by edema. In the nuclei of both these types of cells there were inclusion bodies (figs. 2 and 3). At times the chordae tendineae showed diffuse or nodular thickening and infiltration similar to that in the valve proper.

Fibrinoid vegetations were occasionally encountered (fig. 4). Fibroblasts, mononuclear cells, and endothelial cells in or on the valve at the base of the vegetations contained intranuclear inclusions. Rarely a vegetation must have separated from the valve and become an embolus, since there were infarcts in kidney and lung, in those animals whose heart valves were the seat of vegetations.

The muscle is the part of the heart that is most frequently involved and most seriously altered. In rabbits prepared by injection of acacia into a vein, the myocarditis was distributed equally between atria and ventricles but was much more severe on the right side and was frequently confined to it. On the other hand, in the animals that were given

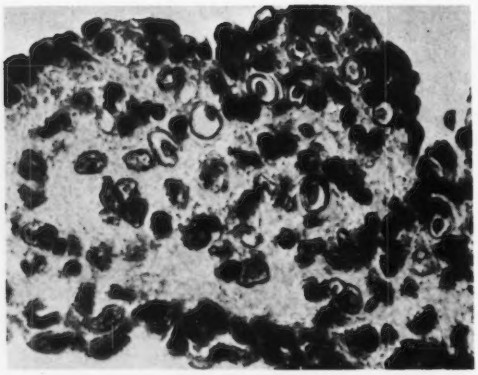

**Figure 2**

*Intranuclear inclusion bodies in the cells of a thickened, fibrotic mitral valve, in a heart infected with virus III. Hematoxylin and eosin stain.*

Pitressin, the left ventricular wall was affected predominantly, especially the inner portions of it and the large papillary muscles. The lesions vary from small nodular collections of lymphocytes and mononuclear cells together with some fibroblastic proliferation to large areas of necrosis with much new growth of fibrous tissue and frequently with deposition of calcium. There is some tendency for the smaller foci of inflammation to be situated beside the blood vessels. Swelling and necrosis of perivascular collagen occasionally take place; the walls of arteries and arterioles never show any definite change. In many of the Pitressin-treated animals a widespread diffuse infiltration of the myocardium without any necrosis and with few nodular aggregates occurred. Intranuclear inclusion bodies were present in a variety of cells in all these lesions (fig. 5).

These experiments left little doubt that a virus was capable of causing pericarditis, endocarditis, and myocarditis, if the heart of the infected animal was subjected to some abnormal situation or, to use the currently popular word, "stress."

The route of entry of infection seems of little importance. Injection of virus into both testes was most commonly employed because the testes could most conveniently be used later for passage and perpetuation of virulent virus, but cardiac localization occurred just as readily in the appropriately prepared animal when the infective agent was introduced by dropping a suspension of it into the nose or injecting it into the skin, beneath the skin, or into a vein.*

The ability of virus III to bring about an inflammatory reaction of all the major structural components of the heart, in the sheathing pericardium and epicardium, the muscles, the endocardium, and the valves having become apparent, one of the several presenting queries was whether or not virus III was unique in this ability. Stated alternately, was it a specific quality of virus III that enabled it to lodge in the heart and there produce inflammatory lesions, or was it an induced susceptibility of the heart that might enable any virus to lodge there and bring about its characteristic host response?

### Susceptibility of the Heart to Invasion by a Variety of Viruses

Five other viruses were used to explore this problem: vaccinia virus, 2 strains of fibroma virus—Shope's original strain A and Andrew's inflammatory strain—pseudorabies virus, and virus myxomatosum. These 5 viruses were especially suitable for this experiment on 2 accounts: first, they readily infect the rabbit, and secondly, they have characteristic histologic identifying reactions. Thus, this strain of vaccinia virus causes an intense necrotizing inflammation. The fibroma virus produces its characteristic fibromatous lesion. The myxoma virus not only produces a myxomatous lesion, but causes a striking and distinctive hypertrophy of cells, and the pseudorabies virus has typical intranuclear inclusion bodies. Since the gum acacia solution had been most successful with virus III in inducing cardiac localization, this method was used to prepare the animals that were in-

*Supernatant fluid of virus-III tissue cultures was used for intravenous injection to avoid embolization by particulate matter in the lungs and to avoid killing the animal by the intravenously toxic material in a ground-up tissue suspension.

ocu.ated with these other viruses by the same intratesticular route. The results of these experiments paralleled our experience with virus III. The incidence of cardiac involvement varied from 60 per cent in the case of the myxoma virus to 80 per cent in vaccinia virus infection and in infection by inflammatory strain of fibroma virus, 70 per cent of the rabbits infected with myxoma and the fibroma strain A had lesions in their hearts. In the control animals that had not been prepared by intravenous gum acacia solution, there was a somewhat higher incidence of cardiac lesions than was the case with virus III. This was perhaps to be expected, however, since these 5 viruses are of a considerably higher degree of virulence than is virus III. It must be stressed, however, that the lesions in the hearts of rabbits that had not been subjected to gum acacia were minimal. It often required considerable search to find them, and they were never of a comparable degree of severity to those in the acacia-prepared animals.

The character of the lesions varied in detail with the peculiarities of the exciting agent, but the general disease picture and the individual lesions were the same in all, myocarditis predominating in all infections. In vaccinia and pseudorabies the valves also were frequently affected. The vaccinia virus tends to produce in the myocardium numerous small, nodular lesions consisting of small foci of necrosis, infiltrated and surrounded by mononuclear and polymorphonuclear leukocytes, but in some hearts there was a diffuse infiltration of large areas of myocardium by leukocytes. In the mitral and tricuspid valves there occurred an interstitial infiltration of leukocytes together with edema and proliferation of fibroblasts, which often resulted in marked thickening of the flap. In the animals infected with the pseudorabies virus, the lesion was again predominantly myocarditis, and except for the presence of the intranuclear inclusion bodies characteristic of this infection, was not dissimilar to that seen in vaccinia. Rows of swollen endothelial cells containing intranuclear inclusion bodies lined

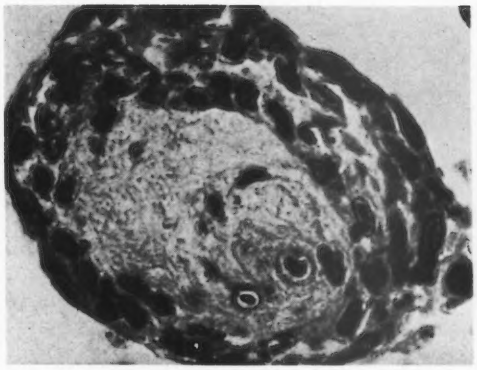

**Figure 3**

*A chorda tendinea surrounded by proliferating cellular endocardium and cells containing typical virus-III intranuclear inclusions. Hematoxylin and eosin stain.*

parts of the atria. The myocarditis of the myxoma group was characterized by the typical myxomatous tissue reaction. Large, irregularly stellate or spindle-shaped basophilic cells with huge pale nuclei in which the chromatin was finely stippled or collected in larger granules at the prominent nuclear membrane replaced extensive areas of myocardium. These cells filled the endocardial crevices and obliterated the columnae carneae, smoothing out the inner surface of the right ventricle. The 2 strains of fibroma virus caused the characteristic proliferation of fibroblasts throughout the myocardium of the right side of the heart. The strain-A lesions were the least pronounced, but the inflammatory strain caused much necrosis and the necrotic areas frequently became calcified.

Inclusion of virus III with the 5 additional viruses gives at least 6 viruses that are capable of infecting the heart of the rabbit. These 6 differ considerably from one another in several characteristics. Virus-III infection is mild. There is no objective sign of it in most instances other than a slight elevation of body temperature for 24 to 72 hours, and the animal always recovers. Pseudorabies virus runs an even shorter course, but the temperature is markedly elevated and death invariably supervenes on the third or fourth day

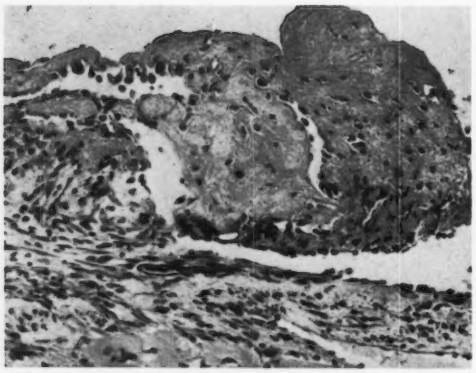

**Figure 4**

*A fibrinoid vegetation on a virus III-infected heart valve. Hematoxylin and eosin stain.*

after inoculation. Myxomatosis is also almost always fatal, but in this disease the animals survive for several weeks, have visible involvement of various mucocutaneous junctions, a blinding purulent ophthalmitis, and, at autopsy, lesions are found in many of the viscera. Vaccinia in the rabbit is a severe and frequently fatal disease. The 2 strains of fibroma virus produce diseases that differ in duration but are never fatal.

The reaction of the host tissues to these 6 invaders is also extremely variable. The lesion of vaccinia is an acute hemorrhagic necrosis with much leukocytic activity, while the effect of strain-A fibroma virus is almost pure proliferation of fibrous tissues with little or no inflammatory response. The other 4 excite reactions that can be classed at various points between these extremes. Physically, the only criterion of differentiation among these viruses is size. The vaccine and myxoma viruses are 2 of the largest filter-passing agents that have been measured; the other 4 are of varying smaller sizes.

All these observations lead to the conclusion that the experiments described indicate most emphatically, in answer to the first question posed, that the ability of a virus to find lodgment in the heart and there to produce morphologic alterations is not a specific property of virus III nor of any group or class of viruses, but is common to many and is dependent, not on the character of the virus, but on the condition of the heart at the time when the virus in the circulating blood passes through it. Attention was therefore next directed to the second aspect of the problem.

### The Factor that Induces the Circulating Virus to Infect the Heart

It has been demonstrated many times and it is obvious from these experiments that inoculated virus almost immediately gains access to the blood stream, and it is by that route only that virus inoculated into the testes can reach the heart. Since it has been shown that it is not a characteristic of the virus that enables it to lodge in the heart, it must be some alteration in the heart that makes it susceptible or favorable to viral growth. At first the only explanation that came to mind to account for the action of gum acacia was the indefinite concept of "overburdening" or "straining" the heart and therefore decreasing its resistance to virus. Simultaneous measurements of venous and arterial blood pressure during injection of acacia failed to show any alterations, and thus doubt was cast on the validity of the "heart strain" theory. To elucidate the localizing mechanism, virus III-infected animals were submitted to a variety of procedures designed to affect the heart in one way or another. Thus, in addition to beta hypophamine (Pitressin), solutions of epinephrine hydrochloride, barium chloride, digitalis, corn syrup, Niketamide ("coramine"), papaverine hydrochloride, and 0.85 per cent sodium chloride were injected intravenously. The last was administered in 100-ml. amounts as rapidly as the fluid could be forced from a syringe through a 20-gage needle. Another group of animals underwent chloroform narcosis.

The results fall into a definite pattern. Those procedures that reduced the supply of oxygen to the heart are followed by a high incidence and a high degree of severity of viral lesions of the heart. Those procedures that are capable of damaging the heart or

altering its function in a variety of ways but that do not directly or indirectly decrease the oxygen available to that organ did not increase the susceptibility of the heart to virus infection.

The anatomic distribution of lesions between the 2 ventricles furnished secondary evidence that a lack of oxygen is of importance in the development of viral lesions of the heart, since it corresponds to the area to which the flow of oxygen is diminished by the different actions of acacia and the drugs constricting the coronary artery. Thus, in the case of constriction of coronary arteries, the right ventricle and the atria are spared because the muscular wall of these chambers is so thin in a rabbit and contain so many endothelial-lined crevices communicating with the cavities that they are less dependent on coronary circulation and may receive a major part of their oxygen and nutriment directly from the blood within them. The thick left ventricle, however, is supplied by the blood flowing through the coronary arteries, and when that flow is diminished, the muscle suffers. The inner portions of the myocardium and the plump papillary muscles of the left ventricle receive the terminal branches of the arteries and are therefore the regions most severely affected by the narrowing of the lumina of these vessels. This narrowing obviously may be brought about by the active contraction of the smooth muscle of the arterial walls that occurs under beta hypophamine[3–5] or barium chloride stimulation,[6] or it may result from the great increase in the intramyocardial as well as the intracardiac pressure that occurs during the period of increased contractile force and acceleration of rate brought about by epinephrine.[7] The elevation of arterial blood pressure that follows the administration of all 3 substances also causes the intramyocardial pressure to rise. In vivo experiments conducted by Johnson and Di Palma[8] have demonstrated that during systole the intramyocardial pressure of the left ventricle exceeds the intraaortic and hence the intracoronary pressures. The coronary arteries are thereby compressed, and the volume of blood

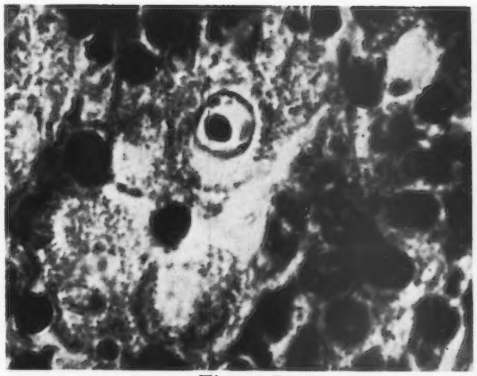

**Figure 5**

*An intranuclear inclusion surrounded by nondescript cells of inflammation in the myocardium of the heart of an animal infected with virus III. Hematoxylin and eosin stain.*

flowing through them to the inner part of the myocardium and the papillary muscles is diminished. As was indicated by Anrep and his associates,[9–12] in strongly beating hearts the volume of blood flowing through the more superficial arteries is reduced by the increase of intramyocardial pressure brought about by the stronger contraction.

The entirely different mechanism by which acacia produces cardiac anoxia explains why the intravenous injection of this substance combined with the inoculation of virus results in lesions predominantly on the right side of the heart. The acacia interferes with the interchange of oxygen between the hemoglobin of the red blood cells and the surrounding fluids and tissues. This action has been well demonstrated by Christie, Phatak, and Olney[13] and has been used to explain the cases of accidental death that followed the use of this substance as a plasma substitute during and following World War I.[14] The greatest dilution of blood and hence the greatest interference with the passing of oxygen from red blood cells to tissue fluid occurs in the right atrium and ventricle as the acacia pours in from the injection site, the marginal ear vein, through the superior vena cava. Not only is the blood reaching the left ventricle more highly oxygenated after passing through the lungs, but also the mixture of blood from

superior and inferior venae cavae has become more complete, has decreased the local concentration of acacia, and has therefore diminished the interference with gas interchange.

The validity of this hypothesis was tested by inoculating animals with virus III and immediately thereafter placing them in an atmosphere deficient in oxygen. The result of this experiment was comparable with those in which acacia, epinephrine, barium chloride, or Pitressin had been used. The incidence of cardiac inflammation was 66.7 per cent. This proves that cardiac hypoxia is a determinant factor in the development of viral myocarditis. That it may not be the only factor is indicated by experiments in which animals were prepared by an intravenous injection of streptolysin O, the hemolytic toxin of streptococcus pyogenes.

### Role of the Hemolytic Streptococcus in Viral Myocarditis

The long-observed association of hemolytic streptococcus infections with bouts of rheumatic heart disease in human beings lends to this pyogenic organism an especial importance in the consideration of cardiac inflammation. The presence of the toxin of streptococcus pyogenes in the blood of virus-infected rabbits also increases the incidence of viral myocarditis. Immediately after the intratesticular injection of the virus, these animals were given a single intravenous injection of a toxin prepared by Dr. Allen W. Bernheimer, of New York University. Virus III was used in these experiments. Sixty-six per cent of these rabbits developed inflammatory lesions in the heart in which virus-III inclusion bodies could easily be identified. The mechanism by which the streptococcus toxin causes this cardiac localization of virus is again not clear. It may be that in some way the toxin produces a myocardial ischemia. It may be that it is a pharmacologic action on coronary circulation similar to that of barium chloride, and may thereby cause a spastic contraction of these arteries that in turn deprives the myocardium of oxygen-carrying blood. In addition it may, like epinephrine, so increase the contractile force of the heart and thus the intramyocardial pressure that blood is prevented from flowing through the smaller arterioles and capillaries. Indirect evidence in favor of this view is the demonstration by Bernheimer and Cantoni that similar preparations of this oxygen-labile hemolysin bring the isolated frog heart to a standstill in systolic contracture. Possibly the toxin interferes with the normal activity of the respiratory enzymes of the muscle cells and thereby produces a cellular hypoxia that allows virus infection. In the heart muscle of some animals, the toxin alone causes minute spots of necrosis that may constitute localized areas of "cardiac hypoxia" that are susceptible to viral infection. Although this substance is strongly hemolytic, it seems unlikely that in the amounts used it brought about any significant intravascular hemolysis, since there were no hemoglobin casts in the kidneys, no hemoglobin in the excreted or bladder urine, and no stain of the aortic intima.

### Viral Heart Disease in Man

The over-all similarity of the experimental viral lesions produced by virus III to the lesions of rheumatic heart disease in man is striking but nevertheless there is no direct evidence for the viral etiology of rheumatic fever. The part played by the hemolytic streptococcus cannot be discounted. But that part might be, as it is in the virus-III carditis, one of preparing the heart for invasion by an unknown virus. That no other animal is susceptible to virus III indicates host specificity. That no virus has ever been isolated from rheumatic hearts by animal inoculation may also indicate host specificity rather than that rheumatic fever is not caused by a virus.

The majority of cases of viral myocarditis or endocarditis in human beings has occurred in patients in whom the cardiac involvement is a complication of a generalized virus disease. There are cases of generalized vaccinia in which there has been a myocarditis and an endocarditis. The salivary gland virus commonly affects the heart as well as many other organs and tissues. All pathologists have had

experience with cases of nonbacterial myocarditis of unexplained origin that have been given names such as "primary interstitial," "idiopathic," "isolated," and "Fiedler's myocarditis." Saphir[15] has recently reviewed 241 cases of such lesions. Myocarditis has occurred during the course of influenza A pneumonia,[16] and in the recent epidemic of "Asian" influenza, we have seen 4 fatal cases in which there was a myocarditis as well as a pneumonitis. To be sure, all of these patients had some preceding cardiac disability. Speculation here centers around the possible hypoxia brought about by the pulmonary consolidation and the possibility that the poor cardiac status might have enabled the virus to localize in the hypoxic heart muscle.


### Summary

A number of filtrable viruses can infect the heart and there produce myocarditis, endocarditis, and pericarditis. However, this action depends on a coexisting deprivation of oxygen to the heart.

### Summario in Interlingua

Un numero de filtrabile viruses pote inficer le corde e producer myocarditis, endocarditis, e pericarditis. Tamen, iste action depende del coexistentia de un stato de privation de oxygeno in le corde.


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# ABSTRACTS

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## PULMONARY DISEASES

**Brenneman, A. R. and Liebow, A. A.: Pulmonary Hypertension.** Yale J. Biol. & Med. 31: 271 (Apr.), 1959.

The usual changes observed in pulmonary hypertension associated with various clinical situations consist of necrosis, fibrinoid changes, and cellular infiltrations of pulmonary arterioles. Whether these changes are the cause or effect of the pulmonary hypertension has not been established. Since these changes do occur in a variety of clinical conditions it has been thought that the sequence might be arterial spasm, hypertension, and ultimate damage to vessels in consequence of either, or both, of the preceding. The various experimental methods used in an attempt to answer this question have consisted of anastomosis of pulmonary to systemic vessels; resection of pulmonary tissue to restrict the output of the right ventricle to a reduced pulmonary arterial bed, and embolization of the pulmonary vascular tree. In this study the isolated lower lobe of the left lung of adult dogs was utilized. Infusions under pressure were made into the isolated arterial vasculature of this lobe accompanied by simultaneous occlusion of the venous drainage of the lobe. In the first group of animals, 10-minute infusions of compatible blood with pressures oscillating between 50 and 100 mm. Hg at the rate of 20 to 60 oscillations per minute were carried out. In the second group, the same procedure was repeated except for a total of 20 minutes of hypertension. In the third group, infusion of 0.9 per cent saline with pressures oscillating between 100 and 150 mm. Hg for a total of 10 minutes was accomplished. The animals were then sacrificed at 3, 5, and 7 days after the induced hypertension. Cultures taken from the lung were sterile. Tissues from the left lung were taken for comparison with those from the right. In none of the groups was there any evidence of vascular lesions. Thromboses of occasional small blood vessels, some hemorrhage into alveoli, and small foci of atelectasis were observed. The failure to produce arterial lesions in these experiments may be related to insufficient rises of pressure in the arterioles; insufficient duration of the hypertension; interruption of nervous pathways due to dissection that might have inhibited vascular spasm; or absence of previous hypertrophy of muscle, which may be necessary before acute vascular changes result from sudden high peaks of pressure. Other experiments must be designed to eliminate these factors.

LEVINSON

**Yoell, J. H.: Bone Marrow Embolism to Lung Following Sternal Puncture.** Arch. Path. 67: 373 (April), 1959.

This paper consists of the presentation of a case of red marrow embolism to small pulmonary vessels in a man who 9 days prior to death had had a sternal marrow aspiration. Death was not attributed to this event. This is the second such case to be reported.

MAXWELL

## RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

**Barger, A. C., Liebowitz, M. R., and Muldowney, F. P.: The Role of the Kidney in the Homeostatic Adjustments of Congestive Heart Failure.** J. Chron. Dis. 9: 571 (May), 1959.

Progressive valvular damage was studied in dogs to determine how nervous reflex changes,

which occur early in heart disease, may affect the accumulation of fluid in congestive failure. Dogs with mild valvular damage (tricuspid insufficiency) showed changes in salt and water metabolism long before overt signs of failure. Plasma volume and total exchangeable sodium were increased. After superimposed pulmonary stenosis and the development of frank failure (right atrial pressure 31 cm. of water), sodium excretion was almost negligible in an 8-hour period. By means of chronic catheterization of 1 renal artery and the separate collection of urine from each kidney, various solutions were studied following direct injection into 1 kidney. Normal dogs and those in frank failure were compared. Results indicated that increased tubular reabsorption of sodium was apparently a major renal abnormality in congestive failure. The role of the renal nerves in the regulation of sodium and water balance was studied by infusing l-norepinephrine intrarenally. At the rate of 1 $\mu$g. per minute or less, sodium excretion on the same side was reduced. Dibenzyline reversed the effect of norepinephrine when infused at the same time and increased sodium and water excretion 50 to 100 per cent (unilaterally) in the dog with mild heart impairment. A marked increase occurred in the reclining dog in frank failure, but not in the upright dog; this suggested further increased sympathetic activity. Hexamethonium produced a smaller increase. The importance of the carotid sinus reflex in sodium excretion was also discussed.

MAXWELL

**Hanley, T., Jowelt, G. H., Kilpatrick, R., and Platts, M. M.: The Role of Carbonic Anhydrase in Renal Reabsorption of Bicarbonate.** J. Physiol. **145: 277 (Mar. 3), 1959.**

Increasing doses of sodium acetazolamide were injected intravenously in human subjects and dogs, following which the effects on the renal excretion of bicarbonate were studied. In man, a systematic relationship was observed between the dose of acetazolamide administered and the rate of renal bicarbonate reabsorption for, as the dose of the inhibitor was increased, bicarbonate resorption by the renal tubules diminished in a characteristic fashion and appeared to approach asymptomatically a limiting value equal to roughly 75 per cent of the initial level. Since the maximum amount of the bicarbonate excreted (in man) was 21 to 29 per cent of filtered load, the authors concluded that the renal tubules reabsorb about 75 per cent of the filtered bicarbonate by 1 or more mechanisms which are not dependent on carbonic anhydrase.

KARPMAN

**Levinsky, N. G., and Berliner, R. W.: Changes in Composition of the Urine in Ureter and Bladder at Low Urine Flow.** Am. J. Physiol. **196:** 549 (Mar.), 1959.

When the ureter and bladder are perfused at flows of less than 1 ml. per minute movements of water, urea, sodium, potassium, chloride, creatinine, and hydrogen ion occur. The magnitude of these changes increases as the rate of perfusion is decreased, or when urine is allowed to pool in the bladder. All movements of water and solute are in the direction of their concentration gradients. In experiments carried out in dogs, these movements were unaffected by changes in antidiuretic activity, anesthesia, or surgical manipulation. Fluid collected from an indwelling Foley catheter draining continuously at a rate of 0.1 ml. per minute may have an osmolality approximately 10 per cent lower than that of the fluid entering the ureter and a urea concentration about 15 per cent lower. When urine is allowed to accumulate in the bladder during 30-minute periods at the same flows, the changes may be 50 to 100 per cent greater. At low urinary flows, the composition of urine collected from the bladder does not accurately represent the composition of the urine as it leaves the kidney.

KAYDEN

## RHEUMATIC FEVER

**Diamond, E. F.: Is There a Rheumatic Constitution?** J. Pediat. **54:** 341 (Mar.), 1959.

Various physical characteristics in rheumatic patients were evaluated and tabulated. Patients with rheumatic fever had no characteristic hair or eye color, a tendency towards a well proportioned body build, a slightly increased tendency towards non-secretion of ABO substance in the saliva, a normal distribution of blood groups and definite hyperextensibility of the metacarpophalangeal joints. Pallor of the skin was found in 52.4 per cent of patients with acute rheumatic fever, but this feature was not a prominent one in patients with inactive rheumatic fever. No evidence of racial susceptibility to rheumatic fever was observed.

KARPMAN

**Feinstein, A. R., and Di Massa, R.: Prognostic Significance of Valvular Involvement in Acute Rheumatic Fever.** New England J. Med. **260: 1001 (May 14), 1959.**

In 359 patients examined at monthly intervals after an attack of rheumatic fever the features of the acute episode were analyzed and correlated with the subsequent cardiac status. All patients studied were kept on continuous antimicrobial

prophylaxis. The follow-up period ranged from 2 to 9 years and averaged 4.7 years. The data suggested that the auscultatory findings during the acute attack of rheumatic fever are of primary importance in predicting the cardiac prognosis. In patients with no auscultatory evidence of murmurs (labelled "no valvulitis") or in whom only a questionable diastolic murmur or an apical systolic murmur was found during the acute attack (labelled "probable valvulitis") a reasonable assurance existed that subsequent heart disease would not develop. Heart disease as a sequel of the rheumatic attack probably will develop in those patients who show evidence of valvular involvement during the acute episode as evidenced by the findings of a definite diastolic murmur, cardiac enlargement, congestive heart failure or pericarditis. The results have obvious clinical and psychologic importance in the management of patients with rheumatic fever.

SAGALL

**Feinstein, A. R., Wood, H. R., Epstein, J. A., Taranta, A., Simpson, R., and Tursky, E.: A Controlled Study of Three Methods of Prophylaxis against Streptococcal Infection in a Population of Rheumatic Children. II. Results of the First Three Years of the Study, Including Methods for Evaluating the Maintenance of Oral Prophylaxis.** New England J. Med. **260**: 697 (Apr. 12), 1959.

The effectiveness of 3 prophylaxis regimens in the prevention of streptococcal infections and recurrences of rheumatic fever over a 3-year period was studied in 391 children and adolescents. All patients had had unequivocal previous attacks of rheumatic fever in the past. The patients were examined monthly in a special clinic. Streptococcal infections were detected by careful bacteriologic and immunologic technics and recurrences of rheumatic fever diagnosed by means of the modified Jones criteria. The regimens investigated consisted of single oral daily doses of 1.0 Gm. of sulfadiazine, potassium penicillin G, 200,000 units per day by mouth, and monthly injections of benzathine penicillin G, 1,200,000 units. The data showed unequivocally that the injections of benzathine penicillin G were more effective than oral sulfadiazine or penicillin for the prevention of streptococcal infections and rheumatic fever and that of the oral preparation of sulfadiazine was as good as, and possibly superior to, penicillin in the dosages employed.

SAGALL

**Johnson, E. E., Mathews, M. J., and Stollerman, G. H.: The Use of Weekly Oral Doses of Sulfamethoxypyridazine for Rheumatic Fever Prevention.** J. Pediat. **54**: 468 (April), 1959.

Sulfamethoxypyridazine (Kynex) was administered once weekly to a group of 30 patients who had had a proven attack of rheumatic fever within a period of 5 years. The drug was well tolerated with only occasional mild and transient side reactions. Sulfonamide blood levels were determined and found to be measurable in most patients even 5 to 7 days after a dose of the drug was administered. During the 247-patient months of the study, no patient was found to have acquired group A streptococcus organisms in the throat. The authors conclude that these observations warrant extension of this study to a larger number of rheumatic fever patients and comparison with similar patients receiving conventional daily oral prophylactic regimens.

KARPMAN

**Marienfeld, C. J., Scheff, G., Hackett, E., and Jones, D.: Studies on the Occurrence of Bacteremia in Rheumatic Fever.** J. Chron. Dis. 9: 344 (April), 1959.

The extensive and contradictory literature regarding the incidence of positive blood cultures in acute and chronic rheumatic fever is thoroughly reviewed. In this study 385 blood cultures from 185 patients with rheumatic fever in various stages were taken, while 124 control cultures were drawn from 100 age-matched and untreated patients, half of whom had nonfebrile illnesses and half of whom had febrile illnesses of various types, with acute rheumatic fever or streptococcal infection excluded. In rheumatic fever patients who had received no therapy a diplostreptococcus was found in 66 per cent in the acute stage, 22 per cent in the convalescent stage, and 10 per cent in the inactive stage. The percentage of positive cultures in the control group including staphylococcal contaminants was 14 per cent in the febrile group and 12 per cent in the nonfebrile group. The difference was significant at the 1 per cent level. The number of positive cultures in patients with rheumatic fever seemed to decrease as a result of 2 factors: the antibiotic medication that had been given and the passage of time from the date of onset of the illness. Fifty of the organisms found in the rheumatic group were completely studied, 45 of these could be grouped and 68 per cent were found to belong to the enterococcus group. Eight per cent were serologically groupable with D serum but did not fulfill all the biological characteristics and 8 per cent were biologically grouped but did not fulfill the serologic criteria. The remaining 16 per cent showed 14 per cent grouped as A serologically and 1 that could not be characterized serologically but that had the A characteristics biologically. The percentage of positive

cultures in the acute rheumatic patients when correlated with earlier reports in the literature seemed to depend on 4 criteria: prolonged period of incubation; subculture through a semiliquid medium; a sufficient dilution of the blood to decrease any possible inhibiting effect that might be present in the blood itself; and the fact that no medication including salicylates had been administered prior to the culture in acute states. The authors suggested that the presence of these organisms in the blood stream may be an indication of their importance in the pathogenesis of the rheumatic process initiated by the group A beta hemolytic streptococcus and it is further suggested that this relationship may exist because of the antigenic similarity which may exist among various groups of streptococci.

MAXWELL

**Saslaw, M. S., Hernandez, F. A., and Randolph, H. E.: Five and Ten Year Follow-up Study of Rheumatic Patients. Role of Climate and Environment.** Am. J. Cardiol. **3:** 754 (June), 1959.

All of the 150 patients with acute rheumatic fever or rheumatic heart disease who had spent 4 months or more in the National Childrens' Cardiac Hospital, Miami, Florida, prior to 1951 were included in a follow-up study carried out mainly by questionnaire. Information was obtained about 133 patients, 93 per cent of whom were living, at an average of 9.3 years following hospital discharge. Recurrence of acute rheumatism was found in 16 per cent of the whole group and in 8 per cent of those who remained in Florida. The use of antibiotic prophylaxis was not mentioned. Heart damage was not found in 44 per cent of the patients and minimal evidence of it was described in 24 per cent. Studies from northern medical centers were cited showing recurrence rates of 28 to 73 per cent, heart damage in 59 to 79 per cent and death rates of 12 to 28 per cent of rheumatic patients. The authors considered the Florida environment to be salubrious for the rheumatism sufferer.

ROGERS

**Taranta, A.: Relation of Isolated Recurrences of Sydenham's Chorea to Preceding Streptococcal Infections.** New England J. Med. **260:**1204 (June 11), 1959.

Sixty patients with a history of chorea and rheumatic fever were placed on continuous antistreptococcal prophylactic agents and followed with monthly throat cultures and serologic testing for streptococcal antibodies at least bimonthly. During the period of observation, ranging from 2 to 67 months, 25 streptococcal infections were detected in 19 patients. Of these, 3 developed definite recurrences of chorea. These 3 cases are presented in detail. The recurrences were not found to be preceded or accompanied by rheumatic polyarthritis or carditis and their clinical onset occurred 3-6 months after the first immunologic evidence of streptococcal infection. These data provide the first available evidence that Sydenham's chorea can follow group A streptococcal infections by an interval longer than that of rheumatic polyarthritis and carditis and further that chorea may in these situations occur in the absence of rheumatic manifestions or signs of rheumatic activity.

SAGALL

**Wilson, M. G., and Lim, W. N.: Short-term Hormone Therapy: Its Effect in Active Rheumatic Carditis of Varying Duration.** New England J. Med. **260:** 802 (April 16), 1959.

Fifty-three attacks of active rheumatic carditis observed In 47 children were treated with steroids. Therapy was given every 6 hours for an average period of 7 days and then terminated abruptly. In all patients the progressive clinical symptoms and signs of active carditis were arrested within 24 to 72 hours after therapy was started. In 91 per cent of the patients the progressive symptoms of carditis were terminated by 1 course of treatment, but in 5 patients a recurrence of carditis required a second 7-day course of steroids for termination. In the 36 patients of this series who received steroid treatment early in the attack (within 21 days) all but 2, in whom the previous cardiac status was unknown, showed no overt evidence of residual cardiac damage. In contrast, in the 17 patients who received treatment late (23 to 150 days) there was little evidence of reversal of the cardiac damage that was present at the onset of therapy, even though progressive signs and symptoms had been terminated. The gross and histologic findings in 38 patients with carditis of variable duration who were observed prior to the advent of antibiotic and steroid therapy and treated only symptomatically were reviewed. These cases showed that with carditis of short duration the lesions were predominantly reversible, whereas with carditis of longer duration extensive irreversible damage was present. The present results with short-term hormone therapy confirmed the authors' previously reported results in 55 patients. They concluded that although short-term hormone therapy will terminate the inflammatory process of active rheumatic carditis regardless of its duration, it is only

with early adequate hormone treatment that residual cardiac damage can be minimized or prevented.

SAGALL

## ROENTGENOLOGY

**Arendt, J., and Rosenberg, M.: Thromboembolism of the Lungs.** Am. J. Roentgenol. 81:245 (Feb.), 1959.

In spite of greater clinical awareness and better methods of prevention (which include early ambulation, vein ligation, and anticoagulant therapy) the incidence of thromboembolism of the lungs has remained high. The incidence of deaths in a general hospital has been given at about 10 per cent and massive embolism has been found in 40 per cent of all hospital necropsies. Emboli of the lungs are of several types. Some are small and give no clinical symptoms and might be classified as incidental. Other emboli of larger size or occurring in multiple sites cause definite clinical symptoms and may be called contributory emboli. A third category, the massive embolus, leads rapidly to asphyxia, anoxemia, and death. Roentgenography or angiocardiography is decisive for diagnosis in a high percentage of cases. Thromboembolism without infarction presents as an abnormal transparency of the involved lung segment (Westermark) with absence of 1 or both of the large hilar vessels. The heart shadow assumes a peculiar shape best described as the "amphoric" type. Thrombi or emboli located slightly more peripherally within the main branches to the pulmonary arteries cause a buckling and aneurysmal widening of the vessels with either a sharp cut-off or taper at the peripheral end of the embolus. Such lesions are compatible with life but may lead to the development of either acute or chronic cor pulmonale. Thromboembolism with infarction does not as a rule present Westermark's sign with increased translucency, since it occurs mostly in a congested lung with dilated bronchial arteries and numerous collaterals. Infarcts represent areas of ischemic necrosis. They are usually located at the periphery of the lung and are rarely wedge-shaped, rather they may be described as "truncated cones" or as "umbrellas." Smaller infarcts frequently have a cuboid or meniscus-like appearance. In the costophrenic angle a "hump-shaped" elevation on the medial side of a small pleurisy is diagnostic. The base of an embolic infarct is sometimes the interlobar fissure line along which it forms a parabolic shadow which is best seen on a lateral roentgenogram.

KITCHELL

**Derra, E., Loogen, F., and Vieten, H.: Difficulties in the Roentgenologic Diagnosis of Spacetaking Processes in the Cardiac Atria.** Fortschr. Röntgenstr. 90:308 (Mar.), 1959.

Tumors and thrombi in the right atrium pose fewer diagnostic difficulties than similar processes on the left side, which usually cannot be visualized even by means of intravenous angiocardiography. Clinical differentiation from mitral stenosis is possible if the mass is mobile and sudden syncope or partial disappearance of dyspnea or murmurs in supine position can be observed.

LEPESCHKIN

**Edling, N. P. G., and Helander, C. G.: Nephrographic Effect in Renal Angiography. An Experimental Study in Dogs.** Acta radiol. 51:17 (Jan.), 1959.

The nephrographic effect in renal angiography was studied experimentally in dogs. It was shown that the effect starts with an increase in the density of the kidney due to contrast filling of the arteries. The phenomenon depends in particular upon a second phase which consists of filtration and excretion of the medium and its accumulation in the tubular cells and ducts. A final phase consists of back diffusion of the contrast medium from tubular cells into renal venous blood.

PAUL

**Esch, D., and Thurn, P.: On the Diagnosis of Pulmonary Hypertension from an Ordinary Roentgen Photograph.** Fortschr. Röntgenstr. 90: 434 (Apr.), 1959.

Prominence of the main pulmonary artery segment and dilatation of the central pulmonary arteries can be caused not only by increased pulmonary pressure but also by increased pulmonary flow. However, in the latter case arterial pulsation is increased and the peripheral arteries are usually also dilated, while in pulmonary hypertension they are narrow. The abrupt change in caliber between the widened lobar and narrowed segmental arteries is the only reliable sign of pulmonary hypertension even in the presence of increased pulmonary blood flow.

LEPESCHKIN

**Grosse-Brockhoff, F., Lohr, H. H., Loogen, F., and Vieten, H.: Puncture of the Left Ventricle for Visualization of Its Outflow Tract.** Fortschr. Röentgenstr. 90: 300 (Mar.), 1959.

Direct percutaneous puncture of the left ventricle was carried out in 26 patients to obtain pressures and to visualize the outflow tract by means of dye injection, after premedication with

procaine amide and in endotracheal anesthesia. An 18-gage needle with a short point was introduced the width of a thumb to the left of the apex beat, in the direction of about 45° from the frontal and sagittal planes. Dye injection was made only after registration of pressures showed that the needle was inside the ventricular cavity; it was carried out in absolute respiratory standstill, and the electrocardiogram recorded during and several minutes after the injection. Extrasystoles appearing singly or in runs were observed in nearly all cases, but ventricular fibrillation appeared only in 1 case, as a result of air embolism. The dye must accordingly be completely free of air. The visualization by direct puncture is of especial value in cases of aortic stenosis, aortic arch syndrome, questionable ventricular septal defects and aortic aneurysms in the vicinity of the heart.

LEPESCHKIN

**Keirns, M. M., and Whiteleather, J. E.: The Angiographic Study of Carotid Insufficiency and Cerebral Ischemia.** Am. J. Roentgenol. 81: 929 (June), 1959.

Invalids from cerebrovascular disease outnumber persons made invalid by malignant disease and constitute a tremendous loss to the country. It is now quite evident that many patients afflicted with "strokes" are victims of thrombosis or stenosis of the cervical carotid artery rather than intracerebral infarction or thrombosis. The authors discuss 1,535 cerebral angiographies made between January 1951 and May 1958. In this series 626 consecutive examinations were done in which the cervical carotid artery and the intracerebral vessels were routinely visualized. Much information was obtained on carotid insufficiency and cerebral ischemia, a condition which most commonly affects the brain and is the second most common cause of death. Stenosis of the carotid artery was seen 3 times more frequently than tumor, 5 times more frequently than aneurysm, and 15 times more frequently than arteriovenous anomaly. Insufficiency of the carotid artery was often clinically indistinguishable from tumor, intracerebral hemorrhage, cerebral embolus, or cerebral atrophy. It may start surprisingly early in middle life (being observed in this series in patients as young as 31 years of age). In the early stage surgical treatment may possibly bring marked improvement. Angiography appears to be safe even in those who have just suffered an acute cerebrovascular accident and should be performed early. Locations where stenosing plaques had been noted were those where complete occlusion most frequently occurred. Four types of stenosing disease were observed and described, each with clinical and pathologic characteristics. A correlation was established between carotid and cerebrovascular stenosis and cerebral atrophy. In examinations made on 482 patients routinely including the carotid bifurcation, since March 1957, 108 cases of stenosis of the carotid artery, 21 cases of thrombosis of the internal carotid artery, 21 cases of either thrombosis or stenosis of cerebral arteries were found.

KITCHELL

**Kuhn, R. A.: Importance of Accurate Diagnosis by Cerebral Angiography in Cases of "Stroke."** J.A.M.A. **169:** 1867 (Apr. 18), 1959.

Exact focal diagnosis in cases of cerebral vascular disease has become essential because of increasingly effective medical and surgical methods of treatment. In the past it was not feasible to determine during life the exact lesion responsible for most clinical strokes. With the advent of safe cerebral angiography, management of cerebrovascular disease has been revolutionized. It is now known that many patients developing strokes do so because of the presence of cervical carotid artery disease which is surgically remediable, and with increased blood flow to the brain there is clinical improvement in many patients. Anticoagulants may be useful in cerebral thrombosis. Hemorrhages can be stopped surgically and atheromatous occlusions can be corrected. The dangers of angiography are much less than the dangers of delayed or haphazard treatment. Cerebral angiography should be considered a vital and routine part of medical management of patients with manifestation of stroke.

KITCHELL

**Moe, R. A., and Hunt, W. H.: A Method for Comparing the Cardiotoxicities of Contrast Media.** Arch. int. Pharmacodyn. **119:**110 (Mar.), 1959.

Cardiotoxicities of cardiographic contrast media were compared in thoracotomized dogs by injecting the media through a nylon catheter threaded through the right carotid artery and manipulated so that its openings were opposite to those of the coronary arteries. The effects of 85 per cent methylglucamine diatrizoate (Cardiografin), 70 per cent sodium acetrizoate and a 26 per cent colloidal suspension of thorium dioxide were studied. When equal volumes and rates of administration were employed, the electrocardiographic tracings obtained following sodium acetrizoate showed a higher incidence

and severity of toxic signs than those after methylglucamine diatrizoate. Thorium dioxide, at the volumes employed, was considered relatively non-toxic.

BRACHFELD

**Nice, C. M., Jr., Menon, A. N. K., and Rigler, L. G.: Pulmonary Manifestations in Collagen Diseases.** Am. J. Roentgenol. 81:264 (Feb.), 1959.

The case records, pathologic data, and roentgenograms were reviewed on 109 patients admitted to the University of Minnesota Hospital from 1942 to 1956 inclusive. Five conditions, namely: polyarteritis nodosa, disseminated lupus erythematosus, scleroderma, dermatomyositis, and rheumatic pneumonitis were included. Collagen diseases in general presented the thoracic signs of pneumonitis, pleural effusion, cardiac enlargement, and the nonthoracic signs of evidence of rheumatoid arthritis as x-ray findings. Polyarteritis nodosa often presented hilar vascular prominence, plus either single or multiple nodules in the lungs. Ileus was often noted in the gastrointestinal examination. Disseminated lupus erythematosus presented a combination of atelectasis and pneumonitis plus polyserous involvement. An associated ileus was often seen. Systemic scleroderma presented fibrosis, emphysema, cardiac enlargement, and ring-like (or cyst-like) shadows or tiny nodulations in the chest films. Aperistaltic esophagus, absorption of phalanges, soft tissue calcification, and ileus with small bowel changes also occurred with this syndrome. Dermatomyositis presented fibrosis, emphysema, cardiac enlargement plus soft tissue calcification, aperistaltic esophagus and small bowel changes at times. Rheumatic pneumonitis presented cardiac enlargement and pneumonitis before or between episodes of failure. It is of interest that in the series of 109 patients the chest x-ray did not contribute to the diagnosis at any time in about 1/3 of the patients. In another 1/3, 1 or 2 abnormalities of the chest appeared at some phase as confirmatory findings which could be considered of help. However, the final 1/3 showed a combination or sequence of roentgen findings which actually led to the suspicion of a collagen disorder.

KITCHELL

**Odman, P.: Percutaneous Selective Angiography of the Superior Mesenteric Artery.** Acta radiol. 51:25 (Jan.), 1959.

A technic for performing percutaneous selective angiography of the superior mesenteric artery by a premodelled radiopaque polythene catheter is described. The latter is introduced by percutaneous transfemoral insertion and under fluoroscopic control the catheter is pushed into the abdominal aorta until the tip is considered immediately caudal to the vessel opening. The tip is directed cranially along the ventral aortic wall until it is caught up in the mouth of the artery. Fluoroscopy aids in differentiating the renal artery from the superior mesenteric artery. Urografin 35 per cent was injected at a rate of 8 to 9 ml. per second using 0.8 to 0.9 ml. per Kg. body weight. A pulmonary injection of 10 to 15 ml. contrast medium confirmed the position of the catheter, since the patient experienced a sensation of warmth throughout the abdomen or in the epigastrium if the injection was made into the superior mesenteric artery. No untoward effects were noted in 10 complete examinations.

PAUL

**Portsmann, W.: Visualization of Abdominal Aortic Aneurysms by means of Catheterization.** Fortschr. Rötgenstr. 90: 190 (Feb.), 1959.

In 1 patient a large aneurysm of the abdominal aorta was visualized by dye injection through a radiopaque catheter introduced through the left brachial artery; this was done before and after resection of the aneurysm and insertion of a plastic prosthesis. This method is preferable to direct puncture of the aorta because of the brittle and sometimes calcified aortic wall; and to retrograde catheterization from the femoral artery, since this method may cause the catheter to be caught in the aneurysm or to dislodge thrombi, and also does not allow information concerning the relation of the aneurysm to the renal arteries.

LEPESCHKIN

**Saltzman, G. F.: Circulation through the Posterior Communicating Artery in Different Compression Tests. A Preliminary Report.** Acta radiol. 51: 10 (Jan.), 1959.

A technic is described whereby the posterior cerebral artery can better be filled during carotid angiography. Bilateral vertebral artery compression was employed at the time of carotid angiography by pressure of the finger introduced immediately above the clavicle and behind the common carotid artery onto the transverse process. The compression of the vertebral arteries forced the blood stream from the carotid siphons to the basilar trunk. Successful compression of the vertebral arteries, although not always possible, was a useful diagnostic aid and facilitated the diagnosis of expanding processes within the area of the posterior cerebral artery.

PAUL

**Sebat, L., Ferrane, J., Ranais, J., and Lenegre, J.: Angiocardiographic Study of Pulmonary Vascular Reactivity During Arterial Obstruction by Means of a Balloon.** Arch. mal. coeur 52:10 (Jan.), 1959.

Inflation of a balloon in an artery supplying the pulmonary lobe or 1 of its distal branches caused in dogs a transient increase in the pulmonary arterial pressure and a generalized pulmonary vasoconstriction which could be demonstrated by angiocardiography. This reaction was not present if the animals were pre-treated with protoveratrine and must therefore have a reflex basis.

LEPESCHKIN

**Stein, G. N., Chen, J. T., Goldstein, F., Israel, H. L., and Finkelstein, A.: The Importance of Chest Roentgenography in the Diagnosis of Pulmonary Embolism.** Am. J. Roentgenol. 81:255 (Feb.), 1959.

The importance of roentgenologic examination in the diagnosis of pulmonary disease needs little emphasis. In many hospitals the frequency with which pulmonary embolism is clinically diagnosed depends largely on the frequency with which the radiologist calls attention to the possibility of this disease. The present discussion deals with pulmonary embolism diagnosed on the basis of clinical, laboratory, or necropsy findings in 90 patients. This is an attack rate of .09 per cent among 10,130 adults admitted during the period of study. Among admissions to the medical service the rate was 1.2 per cent and among surgical admissions 0.6 per cent. Sixty-nine of the individuals recovered from their illness and 21 died during the period of the study. Nine of the deaths were directly due to pulmonary embolism; in other cases pulmonary embolism was contributory or incidental. Seventy-two of these individuals had roentgen examination of the chest and the report represents an analysis of these. Abnormal densities were observed in the roentgenograms of 60 patients. In 12 instances x-ray study of the chest was interpreted as showing no abnormality. Twenty-seven patients were examined within 24 hours of the onset of symptoms and 5 had normal roentgenograms. Twenty-three patients were examined 24-48 hours after the onset of symptoms and 4 had normal chest roentgenograms. Only 1 of the 9 patients with negative chest roentgenograms subsequently showed evidence of infarction by x-ray. These experiences suggest that delayed appearance of roentgenographic densities is relatively uncommon. The most common changes noted were either moderate-size homogeneous or linear densities adjacent to a pleural surface and associated with effusion. Elevation of the diaphragm on the affected side was noted in 21 patients; in 5 instances the elevation of the diaphragm was the only roentgenographic abnormality. The diagnosis of embolism was suggested by the radiologist in only 54 per cent of the entire series. It is felt that the alert radiologist should consider pulmonary embolism in the differential diagnosis of every acute cardiorespiratory illness.

KITCHELL

**Steinberg, I.: Angiocardiography in Diagnosis of Congenital Heart Disease in Infancy and Childhood.** J.A.M.A. 170: 772 (June 13), 1959.

Angiocardiography depends on making a rapid serial roentgenographic examination of the heart and great vessels after a timed intravenous injection of contrast substance. It is not necessary to go through this procedure in every patient with congenital heart disease because the physical, electrocardiographic, and conventional roentgenographic examinations often provide a high degree of accuracy in diagnosis. The more complex types of congenital heart disease may also be difficult to diagnose even after angiocardiography and cardiac catheterization. Fatalities have been reported chiefly in the group of patients with cyanotic congenital heart disease; however, in this series of patients, despite double injections for front and lateral views, only 1 fatality in a child with primary pulmonary hypertension occurred in this series of over 1,500 infants and children. It appeared that the failure to recognize a type of heart disease amenable to surgical repair provided a greater risk than angiocardiography.

KITCHELL

**Steinberg, I.: Roentgen Diagnosis of Anomalous Pulmonary Venous Drainage of Right Lung into Inferior Vena Cava: Report of Three New Cases.** Am. J. Roentgenol. 81:280 (Feb.), 1959.

Roentgenographic study plays a significant role in the diagnosis of anomalous pulmonary venous drainage of the right lung into the inferior vena cava. The anomaly can usually be recognized in the conventional frontal roentgenogram which shows a characteristic multiple-branching vessel increasing in breadth from above downward to merge into a broad crescentic channel adjacent to the right cardiac border. In these cases the left lung appears well vascularized, possibly plethoric, and the right atrium is unduly prominent. It may extend well into the right hemithorax. Asymptomatic patients with partial anomalous drainage of the right lung into the inferior vena cava do not require treatment and

may have long lives. Patients with dyspnea, recurrent pulmonary infections and plethora of the lungs may have an associated cardiac lesion requiring repair. Cardiac catheterization is recommended in such cases. In 1 of the reported cases a huge left diaphragmatic hernia caused dyspnea in a 55-year-old woman. Repair of the hernia resulted in the patient's becoming asymptomatic. While the conventional frontal roentgenogram often discloses the characteristic features of this lesion, angiocardiography may not only confirm and establish the diagnosis but may reveal additional anomalies which may be present.

KITCHELL

**Thurn, P.: Roentgenologic Determination of Cardiac Volume.** Fortschr. Röntgenstr. **90**:290 (Mar.), 1959.

All conventional methods of determination of cardiac volume include the volume of the portion of the great vessels immediately adjoining the heart. According to angiocardiographic studies this volume is 75-130 ml., but it may show great individual variability.

LEPESCHKIN

## SURGERY AND CARDIOVASCULAR DISEASE

**Baglio, C. M., Hunter, W. C.: Calcific Arterial Embolization Accompanying Commissurotomy.** J. Thoracic Surg. **37**:490 (Apr.), 1959.

Four factors are associated with arterial embolization in commissurotomy. These are: previous emboli, atrial fibrillation, thrombosis of the atrial appendage, and a calcific valve. It is pointed out that calcific deposits on the cusps of a healed rheumatic mitral valve are quite friable and easily sloughed off by minimal pressure. The authors report the case of a 42-year-old white woman who never regained consciousness following a mitral commissurotomy and died 4 days postoperatively. The postmortem studies showed a cerebral infarction with occlusion of the right middle cerebral artery at its bifurcation by a hard mass containing calcific material and recent clot. The mitral valve was calcified and there was recent antemortem clot in the left atrium. Since the cerebral vessels were free of sclerosis it was felt that the calcific material represented an embolus from the mitral valve. This hazard has been recognized previously but anatomic accounts of this type of embolism are lacking. The authors feel that calcific embolization represents an additional and definite hazard in mitral commissurotomy.

LEVINSON

**Blount, S. G., Jr., Davies, D. H., Swan, B. M., and Swan, H.: Atrial Septal Defect—Results of Surgical Correction in One Hundred Patients.** J.A.M.A. **169**: 210 (Jan. 17), 1959.

The authors report 125 consecutive patients operated on because of the presence of atrial septal defect of the secundum type. Surgery was done under conditions of hypothermia, inflow-outflow occlusion, and direct-vision open-heart surgery. The present report analyzes the first 100 consecutive cases. There were 7 deaths due to surgery, all in the first 43 patients. In the last 82 patients there have been no deaths. It is suggested that the indication for operation in patients under 45 years of age is diagnostic. Following the second year of life, the earlier the operation is performed the better. Surgery in a relatively asymptomatic child between the ages of 2 and 10 years carries a minimum risk (less than 2 per cent) and in all probability insures a normal cardiovascular system at maturity. With proper methods closure of the defects is almost assured and only a small proportion of patients were not improved subjectively or objectively. The presence of a high pulmonary vascular resistance increases the risk and decreases the gain that can be anticipated.

KITCHELL

**Cohen, D., and Hercus, V.: Controlled Hypothermia in Infants and Children.** Brit. M. J. **1**: 1435 (June 6), 1959.

The authors report their method of producing hypothermia in 50 infants and children undergoing thoracic surgery. They used body surface cooling with the machine circulating water through special rubber blankets. In addition to the rubber blankets, a length of rubber tubing was used as a coil around the neck. Water at 2 to 4 C. was circulated through the blankets and neck coil and the patient's esophageal and rectal temperatures were continuously monitored. The optimum cooling temperature was about 30 C. At any stage, tepid or hot water could be introduced into the system to allow flexibility and ideal control of body temperature. The advantages of this method of hypothermia over other methods are cited.

KRAUSE

**Eiseman, B., Baxter, B. J., and Prachuabmoh, K.: Surface Tension Reducing Substances in the Management of Coronary Air Embolism,** Ann. Surg. **149**:374 (Mar.), 1959.

With increased left heart open surgery and the use of pump oxygenators the problem of air embolism is a timely one. Results of in vitro flow

studies in a hydraulic system revealed that the resistance to the flow of air slugs was greater in a stationary than in a flowing system. Also it has been shown that the introduction of substances which reduce surface tension will decrease this resistance to flow of the air slug. Air slugs arrested at a point of constriction in a stationary system exert a resistance to flow that is proportional to the surface tension of the liquid. It was established in dogs anesthetized with sodium pentothal that 1.5 ml. of air per Kg. body weight injected into the left ventricle resulted in a 95 per cent mortality with extensive coronary blockade, myocardial ischemia and ventricular fibrillation or arrest. With the use of Tween 80, which diminishes the surface tension by 6 per cent, injected simultaneously with the $LD_{100}$ of air into the left ventricle the mortality was reduced to 90 per cent. With the use of Dow Corning Antifoam A, which reduces blood surface tension by 41 per cent, the mortality was reduced to 46 per cent. These findings have several practical implications. With the use of Antifoam A agents in bubble oxygenators some of this material is swept into the blood stream and even though it has been shown to be toxic in other respects it will probably be of benefit by overcoming resistance to flow of air bubbles. This is of particular importance when the pump oxygenator is stopped and the first few beats of the heart may not be strong enough to overcome the resistance and inertia to flow within the smaller vessels. Also on theoretical grounds the continuous flow pump would be more effective in maintaining high coronary perfusion pressure than the intermittent type. Prophylaxis against the harmful effects of air emboli as they appear following rapid decompression in diving and submarine medicine may also be feasible. Although 0.75 ml. of Dow Corning Antifoam B has been injected into the left ventricle of 4 dogs with no visible short or long term neurologic effects, it is obvious that an equally effective but nonparticulate and nontoxic surface active substance would be preferable. Also a much smaller dose would in all probability be effective.

LEVINSON

**Ellis, F. H., Jr., Kirklin, J. W., Swan, H. J. C., LaShane, J. W., and Edwards, J. E.: Diagnosis (or Triloculare-Biventriculare).** Surgery **45**: 1 (Jan.), 1959.

Five surgically treated cases of common atrium (cor triloculare-biventriculare) are reported and discussed. In 4 patients the mitral valve was cleft and in the fifth there was also a cleft in the tricuspid valve. Because clinically these cases closely resembled common atrioventricular canal and hemodynamically total anomalous pulmonary venous drainage, the authors point out the dangers of misinterpreting the findings as indicative of an inoperable form of common atrioventricular canal and overlooking an operable and possibly entirely curable defect. Extracorporeal circulation was employed in the surgical treatment. One patient did not survive operation. The other 4 are now well, but in 1 pulmonary hypertension persists. The technical details of the operative repair are described.

SAGALL

**Gray, I. R.: Mitral Valvotomy in the Young.** Lancet **2**: 1263 (Dec. 13), 1958.

There has been a reluctance to perform mitral valvotomy in childhood because of the risk of operating during active rheumatic carditis and because recurrence of rheumatic activity might be provoked. This report described 3 young patients, ages 12, 14, and 16, with severe mitral stenosis who have had successful operations. The clinical features and operative findings resembled those in adults, but the history of disability was unusually short, probably due to the circulatory needs of adolescence. Symptomatic relief was immediate, and there was a striking increase in height and weight in the months that followed. None had clinical or histologic evidence of active carditis, and rheumatic fever was not provoked by the operation.

KURLAND

**Johnson, J. L.: Postpericardiotomy Syndrome in Congenital Heart Deformities.** Am. Heart J. **57**: 643 (May), 1959.

A syndrome similar to the postcommissurotomy syndrome has been encountered in patients with congenital heart disease following cardiac surgery. The major feature of the syndrome is that of a pericarditis and sometimes an associated pleural effusion or pneumonia. Five patients are presented in detail and the clinical data of 11 patients with varying degrees of severity of this postpericardiotomy syndrome are summarized. There was nothing unusual about the congenital heart lesions in these patients. Of this group only 1 did not recover and his postoperative course was complicated by pulmonary infarction, subacute bacterial endocarditis, and probably a number of small myocardial infarctions. No evidence of rheumatic activity was found and no patient in this series has as yet shown any form of constrictive pericarditis.

SAGALL

**Parsonnet, V., and Bernstein, A.: Routine Cardiac Monitoring During Surgery and a Cardiac-Arrest Team in a General Hospital.** A.M.A. Arch. Surg. 87:303 (Mar.), 1959.

Because of the high mortality rate from cardiac arrest, the authors describe their experiences following the development of a cardiac arrest team and the use of routine cardiac monitoring in all patients undergoing a general anesthetic. The program and equipment are described in detail. During the time the monitors were used on all patients there were 3 episodes of cardiac arrests and in 2 patients the chest was opened within 20 seconds of stand-still. Two of these 3 patients survived; 1 recovery followed pounding on the sternum and the other after cardiac massage. In the third patient, despite the promptness of therapy, spontaneous cardiac activity did not return. Previously, with the use of a monitor applied to poor risk patients only, there had been 2 survivals out of 6 patients with cardiac arrest. Before the use of any monitoring device there were 28 episodes of cardiac arrest with 22 deaths. In addition to achieving a greater survival rate in cardiac arrest with the routine use of monitors, a number of serious arrhythmias were noted and corrected. In 2 patients, sudden severe bradycardias of 20 per minute were corrected with intravenous atropine. Another instance of sudden ventricular tachycardia led to the discovery of a kinked endotracheal tube; the tachycardia had not yet been observed by the anesthetists. On the routine use of cardiac monitor-alarms on all anesthetized patients.

SHEPS

**Perry, J. K., Cordell, A., Johnston, F. R., and Netsky, M. G.: Experimental Cerebral Embolism with Antifoam A.** J. Thoracic Surg. 37: 342 (Mar.), 1959.

This investigation was launched because of the possible hazard of cerebral emboli from Antifoam A (methyl polyriloxane resin), which is the common material used for defoaming blood after its oxygenation in an extracorporeal oxygenator. Tiny antifoam particles have been observed in the reservoir of the oxygenated blood. Although cerebral emboli have been suspected in some of the cerebral complications this has never yet been established. In this study, 8 dogs were used; 5 received injections of Antifoam A in heparinized blood injected into the right carotid artery. A sixth, used as a control, received only heparinized blood. Two additional dogs were used as control for staining methods. One was perfused with liquid Antifoam A. The other was not perfused and was used as a negative stain control. Care was taken not to inject any air bubbles. The opposite carotid artery was occluded manually during injection. Antifoam A was differentiated from fat by the use of osmic acid, which stains fat black, and in these cases the lesions did not become black, indicating they were not fat. They did take on the oil-red O stain, however. All of the animals receiving the Antifoam A manifested abnormal clinical signs and histologic lesions. These were not seen in the control. The macroscopic findings ranged from simple vascular dilatation to frank infarction. The microscopic findings ranged from neuronal changes to infarcts with hemorrhage. One animal died immediately and showed only change in neuronal structure. The lesions were confined to the cortex and chiefly in the parieto-occipital lobes, which are supplied by the terminal leptomeningeal branches of the middle and anterior cerebral arteries. The localization of emboli in these vessels seems to be related to the small angles at which these branch from the main arteries. The findings are very similar to fat emboli except for much less perivascular hemorrhage. There was, however, evidence of increased capillary permeability noted by injected trypan blue staining the brain.

LEVINSON

**Senderoff, E., Blum, L., and Baronofsky, I. D.: A Clinical and Pathologic Analysis of Rupture of Aortic Homografts.** A.M.A. Arch. Surg. 87: 364 (Mar.), 1959.

Three cases are presented of rupture of aortic homografts, 5, 9, and 27 days after surgery. In 1 patient a localized infection with Aspergillus was present in the intima at the site of rupture. The other 2 patients showed inflammation and tissue necrosis localized to the areas of rupture. The remainder of the graft tissue in all 3 patients was normal. These ruptures did not occur at the suture lines. Two of these 3 patients had premonitory symptoms of severe back and abdominal pain, 3 and 12 days, respectively, prior to the fatal disruption. Because of these experiences and because of the great possibility of error in the detailed collection and preparation of homografts, the authors encourage the use of suitable plastic prostheses.

SHEPS

## UNCOMMON FORMS OF HEART DISEASE

**Boss, J. H., and Bechar M.: Myxoma of the Heart. Report Based on Four Cases.** Am. J. Cardiol. 3: 823 (June), 1959.

Four instances of cardiac myxoma, all arising in the left atrium, were encountered among 6,000 autopsies done at the Beilinson Hospital in Israel during the years 1943 to 1957. Three patients

presented mainly severe cerebral embolization, and the fourth had intractable heart failure due to tumor obstructing the mitral orifice. Two had accelerated erythrocyte sedimentation that led to a mistaken clinical impression of subacute bacterial endocarditis, and in none was the correct diagnosis made ante mortem. The finding of epithelial-lined cystic structures in 1 of the tumors, and the usual absence of underlying endocardial disease, led the authors to regard cardiac myxomas as being of neoplastic origin.

ROGERS

## VALVULAR HEART DISEASE

**Barr, C. G., and Bachmann, K.: Differential Diagnosis of Mitral Valvular Disease by Means of Dye Dilution Curves.** Ztschr. Kreislaufforsch. 48: 381 (April), 1959.

After 30 minutes of rest, 2 ml. of a 1 per cent Geigy-blue solution with Decholin and ether were injected into a cubital vein and the light absorption by the dye was registered with an ear oximeter. The time of appearance of the dye (A) from beginning of the injection to the beginning of the dip in the light transmission curve was longer than the time for ether sensation and shorter than that for bitter sensation. The concentration time (C) corresponded to the duration of the descending branch of the dip, the dilution time (D) to that of its ascending branch, projected to the base line. The sum of C and D averaged 16.1 sec. in 18 normal persons, 19.7 sec. in 16 persons with pure mitral stenosis, 45.4 sec. in 13 persons with pure regurgitation, and 40.8 sec. in 17 persons with combined stenosis and regurgitation. The quotient (C-D)/D was 1.71, 1.84, 2.62, and 2.54 in the 4 groups respectively. When dye was injected into the pulmonary artery, A was smaller, but C and D were comparable to those obtained with cubital injection. As long as no decompensation was present, the values for pure mitral stenosis at rest were, therefore, not much greater than those in normal persons, but the presence of mitral regurgitation prolonged concentration and dilution times considerably. The simple method of dye-dilution curves at the ear lobe after cubital injection can therefore be used to evaluate the degree of mitral regurgitation before and after commissurotomy and to differentiate between functional systolic murmurs and those of mitral regurgitation.

LEPESCHKIN

**Bisell, O., Carlberger, G., and Bevegard, S.: The Mechanics of Respiration in Patients with Mitral Heart Disease.** Acta med. scandinav. 162: 277, 1958.

Respiratory resistance and lung compliance were computed in 20 patients with mitral valve disease by plotting respiratory pressure volume curves obtained with an air-filled esophageal balloon and a spirometer. Compliance was defined as the relation of volume change to pressure change between the highest and lowest points of the curve. Each of the patients demonstrated clinical and laboratory findings consistent with a diagnosis of mitral stenosis and in 6 an additional diagnosis of mitral insufficiency was made. The mean values found were: resistance 5.1 cm. $H_2O$/liter/sec. (range 1.8-7.5); compliance 0.11 liter/cm. $H_2O$ (range 0.049-0.15); resistive work (work against non-elastic resistance) 44.8 liter cm. $H_2O$/min. (range 21-77). Thus, these mitral valve patients have lower compliance and higher resistance on the average than do a similar group of normal control subjects. The quotient of inspiratory/expiratory resistance averaged 0.801. Compliance and resistance were plotted against functional class; and although there was wide scatter, the compliance tended to fall and resistance tended to rise in patients with more severe disease. No definite correlations were apparent when the compliance and resistance were plotted against heart volume, vital capacity, functional residual capacity, total lung capacity, degree of pulmonary congestion (determined radiologically) or time since onset of symptomatology. In 7 patients pressure volume curves were constructed during graduated exercise on a bicycle ergometer, and the compliance was found to decrease in 6 of the 7 while in 3 of the patients the resistance fell during the same period.

FREEDBERG

**Blömer, H., and Rudolph, W.: Clinical Criteria for Estimation of Left Atrial Pressure in Mitral Stenosis (Relations between the Intervals Q-I, R-I, II-MOS and Pulmonary Capillary Pressure.** Ztschr. Kreislaufforsch. 48: 350 (April), 1959.

In 81 patients with mitral stenosis the pulmonary capillary pressure, electrocardiogram, femoral arterial pressure, and high-frequency phonocardiogram were registered synchronously during cardiac catheterization. The interval Q-I from the beginning of Q to the beginning of the first rapid component of the first sound averaged 0.06 second and did not exceed 0.07 second in persons without mitral disease. In mitral stenosis, a value of 0.06 to 0.07 second corresponded to a pulmonary capillary pressure at the time of the first sound that of 0.03 second to 23.3 mm., and that of 0.10 second to 28.1 mm. A similar relation was found between Q-I and the mean capillary pressure, and between the interval R-I (from the apex of R in

lead I) and these pressures. This relation is due to the fact that closure of the mitral valve, which is responsible for the first heart sound, takes place when left ventricular pressure exceeds left atrial pressure. The curved shape of this relation is attributed to the concave form of the ascending branch of the intraventricular pressure curve. The interval II-MOS between the beginning of the second heart sound and the opening snap of the mitral valve showed a linear relation to the pulmonary capillary pressure at the time of this snap. This interval was 0.09 second at a pressure of 19.8 mm. Hg and 0.03 second at a pressure of 38 mm. It showed a similar relation to the mean capillary pressure, but the correlation coefficient was smaller. The rectilinear form of the relation is explained by the relatively straight descending branch of the ventricular pressure curve, since opening of the mitral valve can take place only when ventricular pressure becomes smaller than atrial pressure. In complete arrhythmia the aortic and left ventricular pressures are higher after a long diastole than after a short diastole, and II-MOS is longer although the pulmonary capillary pressure may be the same. In tight mitral stenosis without a diastolic murmur the prolonged Q-I may be an important diagnostic clue.

LEPESCHKIN

**Espino-Vela, J.: Rheumatic Heart Disease Associated with Atrial Septal Defect. Clinical and Pathologic Study of 12 Cases of Lutembacher's Syndrome.** Am. Heart J. **57**: 185 (Feb.), 1959.

The clinical and anatomic features of 12 proved cases (11 at autopsy and 1 at operation) of rheumatic heart disease and atrial septal defect are presented. The author points out the relative rarity of this association, despite the high incidence of admissions of individual cases of atrial septal defects and rheumatic heart disease to the National Institute of Cardiology in Mexico. In this series there were 8 females aged 14 to 71 years and 4 males aged 10 to 48 years. The heart was enlarged in all cases with the right atrium the most dilated cavity followed in frequency by hypertrophy of the right ventricle and then the left ventricle. The left atrium was slightly enlarged or normal. In 3 cases the atrial septal defect was so large as to constitute virtually a single atrium. The rheumatic attack was generally severe and in most it was extensive with variable degrees of rheumatic activity. Double mitral lesions were present in all, with mitral stenosis predominating. Tricuspid involvement was found in 7 cases and aortic damage in 3. The pulmonary artery was always considerably larger than the aorta. The extensive nature of the rheumatic disease excluded a congenital origin of the mitral stenosis. Clinically the features were most often typical of severe rheumatic heart disease with multiple valvular lesions. The added presence of atrial septal defect was suspected because of atypical auscultatory findings, morphologic, hemodynamic, and fluoroscopic data, and the presence of right bundle-branch block in the electrocardiogram. In most patients there was clinical evidence of elevated pulmonary arterial pressure and capillary venous hypertension. The physiopathologic interrelationships of these factors are discussed.

SAGALL

**Fleming, H. A., and Wood, P.: The Myocardial Factor in Mitral Valve Disease.** Brit. Heart J. **21**: 117 (Jan.), 1959.

The authors report an analysis of 750 patients with mitral stenosis directed at evaluating the significance of the myocardial factor in this group. All patients with complicating factors such as increased pulmonary vascular resistance, coronary artery disease, systemic hypertension, multiple valve involvement, previous bacterial endocarditis, and continuing rheumatic activity were excluded from the analysis. Only 24 patients were found (3.2 per cent) where myocardial dysfunction rather than mechanical valve obstruction was responsible for the symptoms. The clinical picture was characterized by signs of mild mitral stenosis associated with a long history of fatigue, recurrent heart failure, atrial fibrillation, and systemic embolism. Characteristic cardiac catheterization findings were a low cardiac output and an almost normal left atrial pressure at rest. A constant feature in these patients was atrial fibrillation. Since there was little evidence from surgery, catheterization, or autopsy that a left ventricular myopathy was present, the authors suggested that this clinical syndrome was an unusual consequence of atrial fibrillation, the latter accounting for the low cardiac output, the high incidence of systemic embolism, and the symptoms. Mitral valvotomy did not improve cardiac function nor prevent embolism in these patients, whereas adequate digitalization, reversion to normal atrial rhythm and permanent anticoagulant therapy were helpful.

PAUL

**Goodwin, J. F., Hollman, A., and O'Donnell, T. V.: Ganglion Blocking Agents in Mitral-valve Disease.** Lancet **2**: 1251 (Dec. 13), 1958.

The authors report the findings in 32 observations on 30 patients with mitral disease studied

acutely with hexamethonium during cardiac catheterization. All patients had mitral valve disease, purely obstructive in all but 4 who had significant incompetence. Two had aortic valvular disease and 2 hypertension. There was no evidence of congestive failure. The data are combined with those of 43 cases reported in the literature. In the majority of subjects, the pulmonary artery pressure fell. However, the effect on cardiac output was variable. The pulmonary venous pressure fell in the majority. The occasional fall in pulmonary artery pressure with a rise in cardiac output suggests that methonium is capable of producing a release of pulmonary vasoconstrictor time. However, the effects of ganglionic-blocking agents are complex and often unpredictable, the effects on the pulmonary circulation often being secondary to changes in the systemic circulation. Hence they are unlikely to have wide use in the investigation of the pulmonary circulation.

KURLAND

**Hoffman, J. I. E., and Rowe, G. G.: Some Factors Affecting Indicator Dilution Curves in the Presence and Absence of Valvular Incompetence.** J. Clin. Invest. **38:** 138 (Jan.), 1959.

Dye-dilution curves were constructed by means of a circulation model in which the amount of forward and regurgitant flow could be measured directly in a calibrated flask. When the valves were competent, all the curve parameters examined were markedly dependent on output and central volume. When the valves were incompetent changes made in the size, shape, and elasticity of the proximal chamber entered by the regurgitant jet influenced the curves dramatically. Little distortion of the curve resulted if the proximal chamber was narrow and rigid even in the presence of a large backflow, whereas gross distortion of the curve occurred if the proximal chamber was large and elastic. The authors hypothesize that the distortion of the curve produced by regurgitation is due to dilution and subsequent washout of the dye and that this in turn depends not only on the amount of regurgitant flow but also on the nature of the regurgitant jet and the chamber which it enters.

KARPMAN

**Lyons, W. S., Tompkins, R. G., Kirklin, J. W., and Wood, E. H.: Early and Late Hemodynamic Effects of Mitral Commissurotomy.** J. Lab. & Clin. Med. **53:** 499 (April), 1959.

Hemodynamic data are presented from the first 12 patients to undergo mitral commissurotomy who accepted follow-up right heart catheterization at the Mayo Clinic. Four and one-half to 6 years after operation all 12 patients were alive. Nine have sustained their maximal clinical improvement to the present time. Four of them have reported further slight gains, 2 of them no change, and 3 of them slight losses. Of the 3 patients who had regressed significantly, recatheterization produced clear evidence that restenosis of the mitral valve had occurred. Two of these patients have undergone reoperation and recurrent severe stenosis was indeed found. The average mean pulmonary artery pressure was 52 mm. Hg before operation, 33 mm. Hg 3 weeks after operation, and 29 mm. Hg 1 year postoperatively. The mean pulmonary artery pressure during exercise fell from 68 preoperatively to 56 and then 58 mm. Hg postoperatively. The preoperative resting mean wedge pressure was 28 mm. Hg, which decreased to an average of 17 mm. 3 weeks postoperatively and averaged 18 mm. Hg 1 year postoperatively. Exercise wedge pressures were available in 5 patients before and after operation. The average mean wedge pressure at rest for these 5 was 27 mm. Hg, with a rise to 38 on exercise. One year postoperatively the average mean wedge at rest was 19 with a rise to 30 on exercise. Both at rest and during exercise the calculated total pulmonary resistance was reduced by an average of approximately 45 per cent in the immediate postoperative period and on restudy 1 year later the major portion of the initial reduction was maintained. The pulmonary arteriolar resistance comprised approximately half of the total resistance across the lesser circulation, a proportion which was maintained postoperatively. Of the 12 patients, 8 showed a rise in the resting cardiac index postoperatively, 6 of these being subnormal preoperatively. Of the 10 patients from whom data are available the increase in cardiac index in response to exercise preoperatively was only 12 per cent while in the early postoperative period this increased to 33 per cent and 1 year postoperatively the cardiac index increased 48 per cent in response to exercise. The mitral valve area index of Gorman and Gorman was 0.8 cm.$^2$ preoperatively in this group, 1.2 cm.$^2$ 1 week postoperatively and 1 year postoperatively. Blood pressure averages preoperatively were 114/66 with a mean of 82, increasing postoperatively to 124/65, with a mean of 89 and remained unchanged at the later follow-up date. Total systemic resistance averaged 1,580 dynes second cm.$^{-5}$ preoperatively, 1,460 3 weeks postoperatively and 1,580 1 year postoperatively. The administration of 99.5 per cent oxygen for 6 minutes was followed by a reduction in cardiac output in 18 of 31 compara-

tive determinations and statistical analysis of the reduction in cardiac output and the fall in pulmonary artery mean pressure which resulted from this maneuver revealed that these changes were of a high order of significance. The authors concluded that the hemodynamic data confirmed the clinical impression that most of the improvement to be expected after commissurotomy was likely to occur in the early postoperative period. They believed that the hemodynamic variable that correlates best with the general clinical status of the individual patient is the magnitude of the increase in the cardiac output in response to effort. Of interest also is the fact that those patients with the highest pulmonary artery mean and wedge pressures and highest pulmonary arteriolar resistance before operation received the greatest absolute improvement with respect to these variables.

MAXWELL

**Miller, R., Jr., and Pearson, R. J., Jr., Mitral Insufficiency Simulating Aortic Stenosis: Report of an Unusual Manifestation of Marfan's Syndrome.** New England J. Med. **260:** 1210 (June 11), 1959.

The case of a 27-year-old Negro woman with Marfan's syndrome is presented. The patient also had a history of rheumatic fever and evidence at autopsy of a healed bacterial endocarditis with rupture of 1 of the chordae tendineae producing marked mitral regurgitation and a giant left atrium. In addition to the physical findings of mitral insufficiency there was a rough ejection type murmur along the right sternal border strongly suggesting aortic stenosis. On the atrial wall opposite the mitral orifice a "jet lesion" was found and on this basis it is postulated that the regurgitant stream of blood impinging upon the aortic root simulated a murmur arising from the aortic valve itself.

SAGALL

**Orjebin, P., and Edouard, P.: Osler's Disease Caused by Staphylococcus Aureus Resistant to Antibiotics, Cured after Splenectomy and Appearing after Valvulotomy of Calcified Aortic Stenosis.** Arch. mal. coeur **52:** 17 (Jan.), 1959.

In a 44-year-old male with calcific aortic stenosis, signs of septic endocarditis appeared 6 months after valvulotomy. This condition proved refractory to prolonged treatment with high doses of antibiotics to which the staphylococcus cultured from the patient's blood was sensitive in vitro, but disappeared after splenectomy and did not recur during the following 9 months.

LEPESCHKIN

**Soderholm, G., and Werko, L.: Acetylcholine and the Pulmonary Circulation in Mitral Valvular Disease.** Brit. Heart J. **21:** 1 (Jan.), 1959.

The hypothesis that an active pulmonary hypertension protects the capillary bed from excessive pressure in mitral valve stenosis was tested by studying the action of acetylcholine on the pulmonary circulation in 13 patients. Infusions of acetylcholine (3 to 14.5 mg. per min.) were administered at a constant rate into the pulmonary artery and pulmonary pressures and blood flow were measured at rest and during exercise. Although acetylcholine caused a decrease in pulmonary artery pressure, the effect was equally well demonstrated in patients with an almost normal pulmonary pressure at rest when repeated during mild exercise. The infusions produced a rapid decrease in arterial oxygen saturation, and the authors ascribed this to an increased blood flow through poorly ventilated areas. These poorly ventilated areas could provide a hypoxic stimulus leading to functional restriction of the local vascular bed. If this mechanism were present in mitral stenosis, the vasodilating effects of acetylcholine could be the result of an interference with a definitely established physiologic mechanism rather than any influence on a "protective" vasoconstriction of the pulmonary bed.

PAUL

## VASCULAR DISEASE

**Bahnson, H. T., Spencer, F. C., and Quattlebaum, J. K., Jr.: Surgical Treatment of Occlusive Disease of the Carotid Artery.** Ann. Surg. **149:** 711 (May), 1959.

Twenty-two patients were treated surgically for occlusive disease of the carotid arteries. The symptoms included unilateral impairment of motor or sensory function, syncope, headache, speech disorders, and impairment of vision. The syndrome of unilateral blindness and contralateral hemiplegia was uncommonly observed. In 20 of the 22 patients the occlusive disease was at the bifurcation of the common carotid artery. The lesion was usually atherosclerosis. Diagnosis was considered particularly in cases of episodic neurologic symptoms associated with abnormalities of the carotid pulse or murmurs or thrills over the carotid bifurcation. Arteriography has been used to confirm the diagnosis and no adverse reactions were encountered with this procedure. The surgical procedure used exclusively in this series was thromboendarterectomy. The problem of cerebral ischemia was not encountered because the endarterectomy was usually accomplished within 10

minutes. In 2 patients a cannula bypass was used to maintain cerebral circulation during the procedure. When the obstruction was partial the results were good in those patients having episodic symptoms. When the symptoms were persistent, the results were poor. With complete obstruction in 7 patients, the results were uniformly poor. In 2 patients the involvement was in the innominate or in the left common carotid near its origin from the aorta. These seemed to belong to the group of cases of unknown etiology known as Takayasu disease. A 58-year-old man, who had been operated on 8 years previously, was reported as representative of this disease. In this patient the serologic test for syphilis was positive. Improvement was present only for 4½ months after a bilateral common carotid thrombectomy. Five years ago a frozen-dried homograft was sutured to the side of the ascending aorta and then to the end of the divided innominate artery and there have been no subsequent attacks. A second patient, a 22-year-old girl obtained relief of symptoms following resection of the innominate artery and replacement with a Nylon prosthesis between the innominate and right common carotid artery. It was concluded that endarterectomy is the procedure of choice in treating upper carotid obstruction and bypass for obstruction near the origin of the vessels from the aorta.

LEVINSON

**DeBakey, M. E., Crawford, E. S., Cooley, D. A., and Morris, G. C., Jr.: Surgical Considerations of Occlusive Disease of Innominate, Carotid, Subclavian, and Vertebral Arteries.** Ann. Surg. 149: 690 (May), 1959.

The authors studied 174 patients with manifestations of arterial insufficiency of the cerebrum and upper extremities. Clinically these patients manifested such features as hemiplegia, visual disturbances, and intermittent claudication of the upper extremities. The blood pressure was often difficult to obtain in the arms. Systolic murmurs were frequently heard at the base of the neck. Vertebral artery insufficiency was manifested by cerebellar, cranial nerve, and bilateral motor and sensory disturbances. However, more exact diagnoses could only be made with careful arteriography in all of these patients when this type of lesion was suspected. Of the 174 patients studied, 73 manifested evidence of extracranial arterial occlusion and 63 of these underwent surgery. Ten of these 63 cases were found to have inoperable lesions due to extensive occlusion of the vessels without a patent distal segment. The lesion was usually atherosclerotic and was proximal, distal, localized, or extensive. These patients were treated either by thromboendarterectomy, graft bypass, or a combination of these procedures. Eighty-eight lesions were explored surgically in these 53 patients, 75 of these lesions were segmental and amenable to surgery. In the remaining 13 extensive and complete occlusion of the internal carotid and vertebral arteries made these cases inoperable. In the 75 operations thromboendarterectomy restored circulation in 92 per cent of 37 procedures. Graft bypass restored circulation in 100 per cent of 38 procedures. Crimped Dacron bypass material was used for grafting. The authors described in detail the surgical procedures utilized. Local anesthesia was used to prevent cerebral depression and to permit recognition of cerebral ischemia during the surgical procedure. Barbiturates and opiates were avoided except in very small doses. Neosynephrine was employed intravenously to maintain blood pressure. Temporary shunts were utilized to maintain cerebral circulation. The intravenous injection of procaine must be avoided, especially when it is used locally in the neck to depress bradycardia and hypotension due to reflex action. In 20 per cent of the patients anticoagulants had failed to prevent progression of the disease. In the authors' experience 40 per cent of patients with arterial insufficiency of the cerebrum and upper extremities the occlusive process is of segmental nature and amenable to surgical treatment. It was not always possible to determine with angiography whether bypass, thromboendarterectomy, or both were necessary. This could only be determined by operation. The patients in this series have been followed for periods of over 5 years and the original good results have been maintained.

LEVINSON

**Derrick, J. R., Pollard, H. S., and Moore, R. M.: The Pattern of Arteriosclerotic Narrowing of the Celiac and Superior Mesenteric Arteries.** Ann. Surg. **149:** 684 (May), 1959.

This study was carried out to gain more insight into disturbances of blood flow resulting from atherosclerotic narrowing of the celiac and superior mesenteric arteries. One hundred and ten unselected aortas of patients ranging from 28 to 86 years of age were studied and carefully examined for evidences of arteriosclerosis of the arteries to the abdominal viscera. Forty-one per cent of the celiac arteries examined demonstrated some narrowing secondary to arteriosclerosis. Twenty-one were found to have, at some point within 1.5 cm. of the aortic orifice, a reduction of 50 per cent or more in the calculated cross sectional area of the artery. Narrowing of the superior mesenteric artery was found in 37 per cent of aortas examined.

Abdominal visceral arteriography, at present, offers the only accurate means of preoperative diagnosis. A case is reported in which preoperative insufficiency of the celiac and superior mesenteric arteries was made. The outstanding clinical manifestation was abdominal pain after eating. An abdominal arteriogram was performed by threading a catheter through the femoral artery under fluoroscopic guidance to the orifice of the superior mesenteric artery followed by injection of dye. A reflux of the dye in a cephalad direction demonstrated narrowing of the celiac as well as the superior mesenteric artery. Surgery in this case was successful but complicated by postoperative intestinal obstruction and then sudden unexplained death. In the absence of a demonstrable gastrointestinal lesion, the inability to ingest adequate quantities of food without suffering abdominal pain should lead to a consideration of the presence of visceral arterial insufficiency, particularly if a malabsorption syndrome can be demonstrated. The presence of a systolic murmur to the left and above the umbilicus, as recorded in the case reported here, should afford a clue to the presence of narrowing of the superior mesenteric artery.

LEVINSON

**Edwards, W. S., and Lyons, C.: Problems in Surgery of Occlusive Disease of the Aorta and Iliac Arteries.** Ann. Surg. **149**: 675 (May), 1959.

Arterial insufficiency of the lower extremities due to atherosclerotic occlusive disease is amenable to surgery particularly when it involves primarily the aorta and iliac arteries. Homografts, which were originally used for bypass of the obstructed segments, were difficult to procure and associated with progressive atherosclerotic changes in the wall of the graft, and occasional aneurysmal dilatation and rupture. In the experience of the authors Teflon appeared to be the most ideal arterial graft fiber, especially in the woven form. Forty nine patients with aortic or iliac obstruction were subjected to various reconstructive procedures. Significant improvement occurred in 84 per cent with a postoperative mortality of 6 per cent. Complications consisted of anastomotic leaks, renal complications, and late thrombosis. Renal complications of anuria and oliguria were thought to be due to reflex spasm of the renal arteries, atheromatous emboli, and to intimal dissection of a plaque in the orifice or lumen of the renal arteries. The authors felt that reflex spasm was not a factor. However, they did note that turbulence occurred proximal to the aortic clamp and this could be responsible for loosening of atheromatous material which could then enter the renal arteries. It was suggested that clamping above the renal arteries with more thorough irrigation of the aortic segment might eliminate this problem. Blind endarterectomy of renal artery plaques should not be done because of lack of provision for reattachment of the distal intima. Late thrombosis occurred less frequently in synthetic grafts than in homografts. Although the over-all results were good in surgery for aorto-iliac occlusive disease, the morbidity and mortality rates still make this a serious surgical procedure. It is not recommended for patients with mild claudication or non-progressive disease. Aortography is advised only when definite surgical intervention is contemplated. At present the 3 indications for surgery are claudication sufficiently severe to interfere with the patient's occupation or necessary activities, pregangrenous extremities, and progression of symptoms.

LEVINSON

**Gryska, P. F.: Thromboendarterectomy in the Treatment of Acute Thrombosis of the Femoral and Popliteal Arteries.** New England J. Med. **260**: 807 (Apr. 16), 1959.

The clinical picture of acute thrombosis of the femoral and popliteal arteries is presented. Two cases are reported in detail and the salient clinical data in 6 are tabulated and illustrated. The author believed that the development of arterial thrombosis was secondary to intramural hemorrhages that cause disruption of tissue and liberation of thromboplastic substances, which may initiate the primary thrombosis in the arterial lumen. In selected cases definite therapy by thrombendarterectomy is of value.

SAGALL

**Khanna, S. D.: An Experimental Study of Mesenteric Occlusion.** J. Path. & Bact. **77**: 575 (Apr.), 1959.

Superior mesenteric artery occlusion in rats produced an ischemic intestinal infarction with necrosis of the mucous and submucous portions of the intestinal villi associated with marked blood loss into the intestinal lumen. The muscular spasm occurring with occlusion of the vessel was thought to be due to a neuromuscular reaction mediated through the intrinsic nerve plexuses or a chemical reaction produced by 5-hydroxytryptamine which was released from the degenerating enterochrome cells of the intestine. Neither edema nor alteration of capillary permeability developed except as a late reactive phenomenon. Occlusion of the superior mesenteric vein was more rapidly lethal than was arterial occlusion; this effect was at least partially due to the fact that hemorrhage and stasis of blood was more marked when the vein

was occluded than when the artery was ligated. Release of 5-hydroxytryptamine was thought to induce prolonged hypotension which aggravated the shock caused by the hemorrhage and thus resulted in a rapid deterioration of the animal.

KARPMAN

**Mikkelsen, W. P., and Zaro, J. A., Jr.: Intestinal Angina: Report of a Case with Preoperative Diagnosis and Surgical Relief.** New England J. Med. **260**: 912 (Apr. 30), 1959.

The case of a 62-year-old man with advanced occlusive disease of the aorta and a 2-year history of intermittent, postprandial abdominal pain, occasionally associated with and relieved by vomiting, is presented. A diagnosis of intestinal angina—the syndrome resulting from arteriosclerotic obliteration or narrowing of the gastrointestinal branches of the abdominal aorta—was made. At abdominal exploration the superior mesenteric artery was found to be obstructed by ostial atherosclerosis and its first few centimeters were encased by periaortic cicatrization. Surgical correction of this vascular abnormality resulted in complete relief of symptoms. The authors believed that this case represented the first recorded instance in which the diagnosis of intestinal angina was made preoperatively and in which successful elective endarterectomy of the superior mesenteric artery was performed.

SAGALL

**Murphy, H.: Trypsin in Peripheral Vascular Diseases.** New York State J. Med. **59**: 1973 (May 15), 1959.

The proteolytic enzyme trypsin has been used for about 50 years in the attempt to dissolve neoplasms, inflammatory tissue, and thromboembolic formations. This review and report are based on the treatment of 210 patients with peripheral vascular disease. The drug was used intramuscularly in a 2.5-mg. dosage as aqueous parenzyme. Encouraging results were obtained in patients with chronic varicose ulcers, superficial venous thrombosis, acute phlebitis with ulcers, dermatitis or cellulitis, and acute superficial thrombophlebitis. Fair results were obtained in cases of chronic deep thrombophlebitis with lymphedema, but this group still presented a challenge. Probably irreversible tissue changes inhibit the accessibility of the thrombolytic and antiphlogistic actions of trypsin. Two patients developed generalized urticaria, and there were local reactions in 14 per cent of patients, requiring discontinuation of trypsin injections.

KRAUSE

## CORONARY ARTERY DISEASE

**Dock, W.: Why Are Men's Coronary Arteries So Sclerotic?** J.A.M.A. **170**: 152 (May 9), 1959.

Both genetic and dietary factors are discernible in studies of the cause of coronary atherosclerosis. The coronary arteries in the epicardium have intimal supports of longitudinal muscle lying in a matrix of connective tissue. These vary from person to person but are more developed in males than in females, even at birth. They provide an anatomic basis for earlier lesions in males. Androgens modify the plasma lipid pattern and may also affect the clearing factor and blood coagulability, thus aggravating the risk of coronary sclerosis and thrombosis in males. In view of the marked change in sex incidence of coronary disease in the past 50 years, the suggestion is made that differences in eating, drinking, and smoking may be major factors in the sex difference in coronary disease. Stress may precipitate coronary attacks and probably accelerates lipid deposition and coagulation of blood, but in those persons on diets low in animal fats, stress does not cause atherosclerosis. It appears that the fault lies not in the sex, but in the masculine love for rich food, alcohol, and tobacco. This causes men in our civilization to die chiefly from coronary disease. Osler pointed out over 50 years ago that this is the "nemesis through which Nature exacts retributive justice for the transgression of her laws."

KITCHELL

**Haeger, K., Wallgren, G. R., and Dundas, P.: Studies of the Coronary Circulation. II. Nylon and Polyethylene Tubes as Coronary Artery Prostheses.** J. Thoracic Surg. **37**: 522 (April), 1959.

Attempts to revascularize ischemic myocardium have generally not been successful. In these experiments polyethylene and Nylon replacements of the right coronary artery of the dog have been made. After loosening the right coronary artery from its groove and severing the smaller branches, a ligature was placed in the vessel and openings were made in the portions of the artery proximal and distal to the ligature. Tubes of the above materials varying in size from 0.97 mm. to 2.43 mm. in external diameter were used. These were inserted directly into the proximal and distal openings in the first group; into the proximal and distal openings with an intervening loop of the tube in the second group; and into the distal end of the ligated coronary and into the proximal end of the divided internal mammary in the third group. Seventeen of 27 dogs survived the complete opera-

tion in the first group; 7 of 10 survived in the second group, and all 16 dogs survived in the third group. It was shown that the increased survival rate occurred with decreased time needed to complete the operation. Ventricular fibrillation was the common cause of failure to survive. This apparently was not prevented by infusion of procaine amide. This arrhythmia occurred most frequently within 30 seconds after release of blood flow from the proximal part of the coronary artery. It appeared that when this blood flow was released more slowly, ventricular fibrillation was less likely to occur. In 24 dogs surviving the operation, the tube has been found to be patent in 16 for periods of 4 weeks to 18 months. The use of heparin or silicone coating has not reduced the incidence of thrombosis in these tubes. It would appear that these prostheses remain patent longer in coronary arteries than in peripheral vessels of similar size. The rapid rate of coronary flow and the shaking movements imparted by the cardiac action are listed as possible reasons for this. The insertion of the tube, with the intima intact where the tube is secured, is another possible factor in the relative success obtained.

LEVINSON

**Kaufman, N., Gavan, T. L., and Hill, R. W.: Experimental Myocardial Infarction in the Rat.** Arch. Path. **67**: 482 (May), 1959.

Histochemical and morphologic changes were observed in experimental myocardial infarcts in rats at intervals from 2 to 90 hours after ligation of the coronary artery. Earliest alterations were in fatty degeneration and succinic dehydrogenase activity, both at 4 hours. At 6 and 12 hours, fatty changes were very marked. Only traces of succinic dehydrogenase activity were seen in the infarcted areas by 24 hours. Cytochrome oxidase activity decreased in 12 hours and disappeared entirely in 72 hours. In the central portions of necrotic infarcts, very little fat or enzymatic activity was found, but both persisted at the periphery to the end of the experiment. The authors agreed with others that this suggested that fatty degeneration in myocardial fibers was associated with reversible injury. Diastase-fast-PAS-positive material first appeared at 6 hours and in all the animals by 12 hours. Myocardial fibers showed a slight increase in eosinophilia at 6 hours. By 18 hours necrosis with typical nuclear changes and loss of cross striations was evident. Definite interstitial hemorrhage was observed at 6 hours. The rat was found satisfatcory for the study of sequential myocardial changes.

MAXWELL

**Leighninger, D. S., Rueger, R., and Beck, C. S.: Effect of Glyceryl Trinitrate (Nitroglycerin) on Arterial Blood Supply to Ischemic Myocardium.** Am. J. Cardiol. **3**: 638 (May), 1959.

In order to quantitate the effect of nitroglycerin on the coronary circulation, the volume of blood flow from the distal cannulation of the circumflex artery of dogs was measured. In 43 experiments, this volume was found to have increased an average of 20 per cent 2 minutes following the intravenous injection of 0.6 mg. of nitroglycerin. This effect continued for as long as 10 minutes and could be repeatedly elicited. It was postulated that the normal dog possesses a few intercoronary vessels that become functional only after stimulation, for example by nitroglycerin or by a Beck operation. The authors propose the establishment of the "nitroglycerin unit" as a standard for gaging the action of coronary dilating agents.

ROGERS

**Meesmann, W.: Studies on the Function of Interarterial Coronary Anastomoses in Myocardial Infarction.** Ztschr. Kreislaufforsch. **48**: 193 (Mar.), 1959.

In 45 experiments on 9 dogs the right coronary artery was compressed for 2 to 4 minutes and the flow distal to the point of compression and in the left coronary artery (thermostromuhr method) was registered together with pressures in the brachial artery and the right atrium. Slight compression caused a temporary fall in flow, soon compensated by vasodilatation, while stronger compression caused a decrease in flow of 30 to 40 per cent persisting for the duration of compression and followed by increased flow after release of compression. No change in arterial or atrial pressures occurred, and the flow in the left coronary artery, which would have supplied any anastomotic circulation, did not increase. Greater compression, which caused arterial pressure to fall and atrial pressure to rise because of myocardial failure, did increase flow in the left coronary artery. It was concluded that blood flow through intercoronary anastomoses appeared only when decrease of flow was sufficient to cause myocardial hypoxia, and that the best clinical method to increase intercoronary anastomoses in patients with coronary disease was to subject them repeatedly to mild myocardial hypoxia for short periods of time through controlled exercise.

LEPESCHKIN

**Miller, A. J., and Moser, E. A.: Arterenol Therapy for Shock after Acute Myocardial Infarction and Pulmonary Embolization.** J.A.M.A. **169**: 2000 (Apr. 25), 1959.

A retrospective evaluation of arterenol therapy

for shock after acute myocardial infarction and acute pulmonary embolization was based on 66 patients seen in 1 year at the Michael Reese Hospital in Chicago. Fifty-five patients had shock following myocardial infarction. Eleven had shock following pulmonary embolization. Arterenol seemed to be the therapy of choice in severe cardiogenic shock and significantly improved the prognosis. Where manifest congestive heart failure was present with the shock, prognosis was poor, and full digitalization, preferably by the intravenous route, should accompany arterenol therapy. The earlier treatment was begun in the shock period, the more effective it became. Hypotension persisting after relief of the pain of acute infarction had been relieved may require treatment but vasopressor drugs, which can be administered subcutaneously or intramuscularly, should be effective in most of these cases. More data are needed on shock complicating pulmonary embolization before definite conclusions as to the effectiveness of vasopressor therapy can be drawn.

KITCHELL

**Nickel, S. N., and Gale, H. H.: Altered Prognosis with Cardiac Massage.** J.A.M.A. **170:** 23 (May 2), 1959.

In 2 instances patients with myocardial infarction collapsed suddenly and became pulseless. Immediate thoracotomy with rhythmical manual compression of the heart was performed plus intracardiac injection of 0.5 ml. of a 1:1,000 aqueous solution of epinephrine. Ventricular fibrillation was restored to normal rhythm by the use of an electric defibrillator and both patients survived without signs of injury to the brain. It is pointed out by the authors that although cardiac massage is thought to be a relatively new procedure, it was first attempted in 1874 and the first successful resuscitation was performed in 1902. It appears that this method of resuscitation, if applied promptly, improves the prognosis of patients with acute myocardial infarction who become suddenly pulseless.

KITCHELL

**de Oliveira, J. M., Carballo, R., and Zimmerman, H. A.: Intravenous Injection of Hyaluronidase in Acute Myocardial Infarction: Preliminary Report of Clinical and Experimental Observations.** Am. Heart J. **257:** 712 (May), 1959.

In 6 patients with acute myocardial infarction and in 7 dogs with experimentally induced acute occlusion of the coronary artery, the intravenous injection of hyaluronidase appeared to have beneficial effects. In all of the patients the S-T segments shifted toward normal within 2 to 24 hours. In 5 patients these changes occurred before the seventh hour. This rapid change was believed to be exceptional and not to be expected under other conditions. Similar results were found in the studies on animals. Hyaluronidase in acute myocardial infarction appears to reduce the intramyocardial edema resulting from acute coronary artery occlusion, either by spreading the edematous process or by increasing capillary reabsorption or both. Although the results of this study are very promising the authors emphasize the need for further investigation before hyaluronidase can be accepted as an efficient drug in the management of acute myocardial infarction.

SAGALL

**Pader, E., and Levy, H.: Effect of Isoniazid in Angina Pectoris.** J.A.M.A. **170:** 157 (May 9), 1959.

Isoniazid was administered over periods of 3 weeks to 20 patients who had had angina pectoris for at least a year. The dosage was 300 mg. a day in 3 divided doses of 100 mg. each. The study was prompted by the striking relief of anginal pain by iproniazid (Marsilid) and the possible use of its less toxic analogue, isoniazid. In the 20 patients studied, 16 patients (or 80 per cent) had no benefits so far as their angina was concerned. Two patients (or 10 per cent) noted slight improvement in capacity for effort, but side-effects compelled discontinuation of the drug. In only 1 patient was sustained improvement noted while on isoniazid, and this drug appeared to be of little value in the treatment of the anginal syndrome.

KITCHELL

**Rakov, H. L.: Specific Syndromes of Coronary Insufficiency and Allied Cardiopathy.** New York State J. Med. **59:** 1965 (May 15), 1959.

The author classifies the specific syndromes of coronary insufficiency into 7 categories. 1. Potential coronary artery insufficiency: coronary artery disease unaccompanied by ischemic phenomena. 2. Provisional coronary artery insufficiency: coronary artery disease with ischemic symptoms and alterations prevented by provisional collateral circulation. 3. Paroxysmal acute coronary artery insufficiency: coronary artery disease with brusque, transient, insufficient coronary circulation and variable focal ischemic myocardial lesions. 4. Prolonged acute, physiologic, nonocclusive coronary artery insufficiency, negligible coronary artery disease with extrinsically provoked, abrupt in onset, prolonged, coronary insufficiency and focal myocardial ischemic subendocardial necrosis. 5. Pro-

longed acute partial occlusive coronary artery insufficiency; patent stenotic lesions of the coronary arteries with dimished total coronary blood flow and myocardial ischemic lesions which usually result in confluent, circumferential subendocardial necrosis. 6. Prolonged acute occlusive coronary insufficiency: coronary artery disease with acute occlusive lesions and massive ischemic myocardial necrosis. 7. Permanent coronary artery insufficiency; marked stenotic coronary artery disease with multiple old occlusions and extensive myocardial fibrosis. This classification of morbid conditions giving rise to the syndromes of coronary artery disease is presented in the hope of promoting consistency in the connotations of coronary insufficiency.

KRAUSE

**Rieger, P.: Contribution to the Understanding of Rudimentary Anterior Myocardial Infarction.** Ztschr. Kreislaufforsch. **48**: 336 (April), 1959.

Holzmann attributed a transient electrocardiographic pattern consisting of slight S-T elevation with terminal inversion of the T wave without QRS changes in leads $V_1$-$V_5$ to "rudimentary" or spotty infarction located in the subepicardial muscle layers of the anterior wall. In 4 patients who had shown this pattern, small areas of myocardial necrosis of fibrosis inside the anterior wall, located nearer the endocardial surface, were found at autopsy. In 2 other patients extensive infarction of the anterior wall was found, 1 had pericarditis and 1 left ventricular hypertrophy without myocardial necrosis; in these 4 patients the T wave was inverted also in lead $V_6$. One patient had massive pulmonary embolism (in this case inverted T waves and borderline deep Q waves appeared in leads II and III). One patient had carcinoma of the gallbladder with jaundice and moderate coronary sclerosis, but a normal myocardium.

LEPESCHKIN

# NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, N.Y.

Telephone Gramercy 7-9170

### Associations Provide $67,180 To Supplement National Research

The Iowa Heart Association has provided $16,380 to supplement the Association's national research support program for the 1959-60 fiscal year, bringing to $67,180 the allocations made by affiliates and chapters for this purpose as of January 1, 1960.

These sums, which are in addition to amounts regularly assigned by Heart Associations for national research, have aided in underwriting a record total of approximately $3,300,000 awarded by the AHA National Office for the 1959-60 fiscal period.

### 1959 Annual Report Issued; Projects Future Tasks, Goals

The recently issued 1959 Annual Report of the American Heart Association is entitled "Perspective for the Sixties." It reviews the Association's past accomplishments as the basis for projecting the tasks and goals of the future.

With funds earmarked for research from the 1959 Heart Fund campaign, the Association and its affiliates and chapters will have, in the past 12 years, channeled nearly $50 million into scientific research, according to the report.

### Blood Procurement Statement Issued by Association

A statement to be used as a guide in programs of blood procurement for open heart surgery has been distributed by the American Heart Association to its affiliates and chapters.

The statement points out that Heart Associations may best serve in this area by cooperating with other community agencies in their blood procurement programs; by publicizing the need for blood; by enlisting volunteers in various donor plans; and by utilizing medical members as speakers to explain the need to the community.

### Academy of Pediatrics Sponsors Cardiology Course

A postgraduate course in "Pediatric Cardiology—Congenital Heart Disease," sponsored by the American Academy of Pediatrics, will be given by the faculty of the Mayo Foundation Graduate School at the University of Minnesota, Rochester, March 30 through April 1, 1960. The course will be under chairmanship of James W. DuShane, M.D., of the Mayo Foundation, who is also Vice-Chairman of the Executive Committee of the AHA Council on Rheumatic Fever and Congenital Heart Disease. Fees for the course are $40 for Academy members and $60 for non-members. The complete program and registration forms are available from the Academy, 1801 Hinman Avenue, Evanston, Illinois.

### Congenital Cardiac Defects Evaluation Booklet Revised

The Association's 32-page reference booklet for practicing physicians on evaluation and management of congenital cardiac defects has been revised under the new title, "Evaluation and Management of Congenital Cardiac Defects—A Physician's Guide." Copies are available without charge from local Heart Associations or from the American Heart Association.

Previously titled, "Congenital Cardiac Defects, a Physician's Guide for Evaluation and

Management," the booklet is intended to help the physician determine when referral to a cardiologist is required.

## Meetings Calendar

April 1-3: American Society of Internal Medicine, San Francisco. R. L. Richards, 350 Post Street, San Francisco 8, Calif.

April 3-6: American Surgical Association, White Sulphur Springs, W. Va. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 4-9: American College of Physicians, San Francisco. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

April 11-16: American Association of Anatomists, New York. Louis B. Flexner, University of Pennsylvania Medical School, Philadelphia 4, Pa.

April 11-15: American Physiological Society, Chicago. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D. C.

May 1-2: American Society for Clinical Investigation, Atlantic City. S. J. Farber, 550 First Ave., New York 16, N. Y.

May 3-4: Association of American Physicians, Atlantic City. P. B. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 11-13: American Association for Thoracic Surgery, Miami Beach. H. T. Langston, 7730 Carondelet Ave., St. Louis 5, Mo.

May 23-28: American College of Cardiology, Indianapolis. Philip Reichert, 2709 Empire State Bldg., New York 1, N. Y.

June 8-12: American College of Chest Physicians, Miami Beach. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Ill.

June 11: International Cardiovascular Society, North American Chapter, Miami Beach. P. T. DeCamp, 3503 Prytania St., New Orleans 15, La.

June 13-17: American Medical Association, Annual Meeting, Miami Beach. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

August 8-11: National Medical Association, Pittsburgh. John T. Givens, 1108 Church Street, Norfolk, Va.

August 21-26: American Congress of Physical Medicine and Rehabilitation, Washington, D. C. Mrs. Dorothea C. Augustin, 30 N. Michigan, Chicago 2, Ill.

September 11-15: International College of Surgeons, New York. Max Thorek, 850 W. Irving Park Road, Chicago 13, Ill.

September 27-30: American Roentgen Ray Society, Atlantic City. Hugh Jones, 20 N. Wacker Drive, Chicago 6, Ill.

## Abroad

May 2-11: Pan American Medical Association Congress, Mexico City. Joseph J. Eller, 745 Fifth Ave., New York 22, N. Y.

May 6-8: International Congress of Phlebology, Chambery, France. J. Marmassee, 3 Rue de la Republique, Orleans, Loiret, France.

May 15-18: International College of Surgeons, International Congress, Rome. Secretariat, 1516 Lake Shore Drive, Chicago 10, Ill.

May 30-June 3: Asian-Pacific Congress of Cardiology, Melbourne, Australia. A. E. Doyle, Alfred Hospital, Melbourne S. 1, Victoria, Australia.

June 2-4: International Symposium on Drugs Affecting Lipid Metabolism, Milan, Italy. Prof. S. Garattini, Institute of Pharmacology, Via A. del Sarto 21, Milan, Italy.

August 14-20: Inter-American Congress of Cardiology, Rio de Janeiro. Magalhaes Gomes, Av. Nilo Pecanha, 38, Rio de Janeiro, Brazil.

August 24-27: International Congress of Internal Medicine, Basel, Switzerland. Secretariat, 13, Steinentorstre, Basel, Switzerland.

August 28-September 1: International Congress on Diseases of the Chest, Vienna. Murray Kornfeld. American College of Chest Physicians, 112 E. Chestnut Street, Chicago 11, Ill.

September 1-3: First International Congress of Nephrology, Geneva. G. Richet, 149 Rue de Sevres, Paris 15, France.

September 4-10: International Society of Hematology, Tokyo. J. L. Tullis, 1180 Beacon Street, Brookline 46, Mass.

September 18-25: Euporean Congress of Cardiology, Rome. V. Puddu, Clinica Medica, University of Rome, Italy.

**1962: Fourth World Congress of Cardiology, Mexico City. I. Chavez, Ave. Cuauhtemoc 300, Mexico, D. F.**

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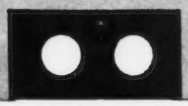
*Just two tablets*  *at bedtime*

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# Circulation

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MARCH 1960
VOL. XXI NO. 3
PART TWO

# Circulation

AN OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Selected List of
Research Training Programs
Supported by the National Heart Institute
National Institutes of Health
Public Health Service
Department of Health, Education and Welfare

INDEX TO LISTED PROGRAMS ON BACK COVER

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## INTRODUCTION

In order to acquaint persons interested in cardiovascular research training with the wide variety of opportunities that are available, the following list of training programs supported by the National Heart Institute is published. The list is a selected one, comprising training programs of particular interest to the readers of this Journal. Not only are there other training programs supported by the National Heart Institute, but other Institutes of the National Institutes of Health also support training programs in their special fields. For example, research training in such preclinical sciences as physiology, biochemistry, anatomy, pathology, pharmacology, etc., are mainly supported in the Division of General Medical Sciences of the National Institutes of Health; the National Heart Institute supports training programs in preclinical departments only when there is special emphasis on cardiovascular research. Further information regarding these other programs may be obtained by writing the Director of the relevant Institute or Division at Bethesda 14, Maryland.*

The National Heart Institute also supports training in cardiovascular research fields by awarding Public Health Service Fellowships. They are awarded for specialized training or when, for any of a number of reasons, the department of the applicant's choice does not have a training grant. The fellowships are awarded competitively on proper application by the individual seeking training. For further information about Public Health Service Fellowships in the cardiovascular and other fields, write to the Division of Research Grants, Bethesda 14, Maryland.

The principal emphasis in all programs is on research and academic training; clinical responsibilities and clinical training are limited to those related to the research goals of the program. Trainee stipends tend to be the same in all programs; they are parallel with those of Public Health Service Fellowships which are graduated according to the stage of training, with dependency allowances. For further information regarding individual programs, or for actual application, the program director should be communicated with directly at his institution. When a training grant has been awarded by the National Heart Institute its conduct, including the policy of candidate selection, is the responsibility of the program director and his sponsoring institution.

It is planned to publish this list of the National Heart Institute cardiovascular research training programs annually, as long as it is deemed useful. Additional copies may be obtained free of charge by writing the Grants and Training Branch, National Heart Institute, Bethesda 14, Maryland.

*National Cancer Institute, National Institute of Allergy and Infectious Diseases, National Institute of Arthritis and Metabolic Diseases, National Institute of Mental Health, National Institute of Neurological Diseases and Blindness, National Institute of Dental Research, Division of General Medical Sciences.

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## I. BASIC SCIENCE DEPARTMENTS

### ANATOMY

**1. Dr. Albert I. Lansing**
Department of Anatomy
University of Pittsburgh
Schools of Health Professions
Pittsburgh 13, Pennsylvania

Predoctoral training in anatomy with special research emphasis on cellular aging, electron microscopy, and cytochemistry. *Number of traineeships: 8; Prerequisites: B.A. or B.S.; Duration: 3-4 years.*

**2. Dr. S. R. M. Reynolds**
Department of Anatomy
University of Illinois College of Medicine
1853 West Polk Street
Chicago 12, Illinois

Training in embryologic and perinatal cardiovascular physiology and anatomy, with facilities for cineangiography in the study of hemodynamics, including the study of the fetus in utero. *Number of traineeships: 4; Prerequisites: B.A., B.S., M.D. or Ph.D.; Duration: 1-3 years.*

### BIOCHEMISTRY

**3. Dr. William C. Boyd**
Department of Biochemistry
Boston University School of Medicine
80 E. Concord Street
Boston 18, Massachusetts

Training in human and medical genetics including the necessary course work and laboratory techniques to perform supervised independent research on cardiovascular and other related problems. *Number of traineeships: 2; Prerequisites: B.A., B.S., M.D. or Ph.D.; Duration: 2 or more years.*

**4. Dr. Fred A. Kummerow**
Department of Food Technology
University of Illinois, College of Agriculture
220 Animal Sciences Laboratory
Urbana, Illinois

Training in the nutrition, chemistry and biochemistry of the lipids with special emphasis on the relation of lipids to atherosclerosis and circulatory disorders. *Number of traineeships: 5; Prerequisites: B.S. in chemistry; Duration: 3 years.*

**5. Dr. Irvine H. Page**
Research Division
The Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation
2020 East 93rd Street
Cleveland 6, Ohio

Training in biochemical research by participation in projects generally concerned with the biochemistry of atherosclerosis. *Number of traineeships: 3; Prerequisites: M.D. or Ph.D.; Duration: 2 or more years.*

**6. Dr. Abraham White**
Department of Biochemistry
Albert Einstein College of Medicine of Yeshiva University
Eastchester Road and Morris Park Avenues
New York 61, New York

Training in biochemistry with special emphasis on physiologic biochemistry, enzymology and lipid metabolism. *Number of traineeships: 4; Prerequisites: M.D. or Ph.D.; Duration: 2 or more years.*

### GENETICS

**7. Dr. Charles M. Woolf**
Department of Genetics
University of Utah
Salt Lake City 12, Utah

Formal training in basic and medical genetics with research opportunities in cardiovascular and related problems. *Number of traineeships: 3; Prerequisites: B.S. or A.B.; Duration: 3 years.*

### PATHOLOGY

**8. Dr. Gustave J. Dammin**
Department of Pathology
Peter Bent Brigham Hospital
721 Huntington Avenue
Boston 15, Massachusetts

Research training in pathology with special emphasis on the pathogenesis of pulmonary vascular disease and transplantation of the kidney, applying biophysical methods, fluorescent antibody techniques, etc. *Number of traineeships: 2; Prerequisites: M.D.; Duration: 2-3 years.*

**9. Dr. Russell S. Fisher**
Division of Forensic Pathology
University of Maryland School of Medicine
700 Fleet Street
Baltimore 2, Maryland

Training in research and practice of forensic pathology and toxicology with special research interests in sudden and traumatic deaths. *Number of traineeships: 2 in toxicology, 3 in pathology; Prerequisites: A.B. or B.S. for toxicology, M.D. for pathology; Duration: toxicology 2-3 years, pathology 1-2 years.*

**10. Dr. S. E. Gould**
Department of Pathology
Wayne State University College of Medicine
1401 Rivard Street
Detroit 7, Michigan

Training in cardiovascular pathology with research interests in unusual forms of cardiac disease. *Number of traineeships: 1 or 2; Prerequisites: M.D.; Duration: 6-12 months.*

**11. Dr. Russell L. Holman**
Department of Pathology
Louisiana State University
1542 Tulane Avenue
New Orleans 12, Louisiana

Training and research experience in pathology, with emphasis on aging and cardiovascular-renal disease, principally as related to atherosclerosis and hypertension. *Number of traineeships: 3; Prerequisites: Ph.D. in chemistry, physics, or biology, or M.D. with 1 year in pathology; Duration: 1-3 years.*

**12. Dr. William E. Jaques**
Department of Pathology
University of Oklahoma Medical Center
801 Northeast 13th Street
Oklahoma City 4, Oklahoma

Training in pathologic research methodology and clinical pathology with research emphasis in cardiopulmonary and cardiorenal problems. *Number of traineeships: 3 Prerequisites: M.D.; Duration: 2-4 years.*

**13. Dr. Averill A. Liebow**
Department of Pathology
Yale University School of Medicine
301 Cedar Street
New Haven, Connecticut

Development of pathologists for investigation and teaching careers, with special emphasis on cardiopulmonary pathology and pathophysiology. *Number of traineeships: 3-4; Prerequisites: M.D. or Ph.D.; Duration: 3-5 years.*

## PHARMACOLOGY

**14. Dr. George H. Acheson**
Department of Pharmacology
University of Cincinnati
College of Medicine
Eden and Bethesda Avenues
Cincinnati 19, Ohio

Training in laboratory research on cardiac functions and their abnormalities, and on the influence of drugs on the heart and related tissues. *Number of traineeships: 2; Prerequisites: B.A., B.S., M.D. or Ph.D.; Duration: 1-3 or more years.*

**15. Dr. Walter M. Booker**
Department of Pharmacology
Howard University School of Medicine
Washington 1, D. C.

Graduate training in pharmacology leading to the M.S. degree with emphasis on cardiovascular pharmacology. *Number of traineeships: 5; Prerequisites: B.S. or M.D.; Duration: 1-2 years.*

**16. Dr. R. P. Walton**
Department of Pharmacology
Medical College of South Carolina
16 Lucas Street
Charleston 16, South Carolina

Research training in experimental cardiovascular pharmacology, with collaborative projects in the areas of anesthesiology, medicine and surgery. *Number of traineeships: 5; Prerequisites: B.S. or M.D.; Duration: 2-5 years.*

## PHYSIOLOGY

**17. Dr. Bernard C. Abbott**
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405 Hilgard Avenue
Los Angeles 24, California

Training in comparative cardiovascular physiology including formal and laboratory courses, and seminars on biophysics and physiology of contractile tissues. *Number of traineeships: 8; Prerequisites: B.A., B.S. or Ph.D.; Duration: 1-3 years.*

**18. Dr. Chandler McC. Brooks**
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450 Clarkson Avenue
Brooklyn 3, New York

Predoctoral and postdoctoral training in research techniques of cardiovascular physiology with research emphasis on electrophysiology. *Number of traineeships: 4; Prerequisites: A.B., B.S., M.D. or Ph.D.; Duration: 1-3 years.*

**19. Dr. Robert E. Forster**
Department of Physiology
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Graduate School of Medicine
3320 Walnut Street
Philadelphia 4, Pennsylvania

Training in pulmonary physiology for the graduate M.D. including basic course work and guided experience in physiological research. *Number of traineeships: 2; Prerequisites: M.D.; Duration: 2 years.*

**20. Dr. George P. Fulton**
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675 Commonwealth Avenue
Boston, Massachusetts

Training in vascular physiology and micro-circulatory biology, emphasizing biochemical and biophysical aspects. *Number of traineeships: 4; Prerequisites: B.S. or Ph.D.; Duration: 3 years.*

**21. Dr. Arthur C. Guyton**
Department of Physiology and Biophysics
University Medical Center
University of Mississippi
Jackson, Mississippi

Training in cardiovascular physiological research for selected medical students and others wishing to pursue research training simultaneously with and beyond their medical studies. *Number of traineeships: 3; Prerequisites: B.S., M.D. or Ph.D.; Duration: 3 years.*

**22. Dr. C. Adrian M. Hogben**
Department of Physiology
The George Washington University
1339 H Street, N. W.
Washington 5, D. C.

Predoctoral training in physiology with particular emphasis on transport phenomena, electrolyte metabolism, and the peripheral circulation. *Number of traineeships: 2; Prerequisites: B.S. or B.A.; Duration: 3-4 years.*

**23. Dr. Howard M. Klitgaard**
Department of Physiology
Marquette University School of Medicine
5618 North 15th Street
Milwaukee 3, Wisconsin

Training in physiology, with emphasis on general circulatory physiology, including courses in higher mathematics and biophysics, and facilities for use of radioisotopes. *Number of traineeships: 8; Prerequisites: B.A. or Ph.D.; Duration: 1-4 years.*

**24. Dr. Robert F. Pitts**
Department of Physiology
Cornell University Medical College
1300 York Avenue
New York, New York

Postdoctoral research training in the principles of homeostasis of the water and electrolyte content of the body including the distribution of ions in cells and extracellular fluid. *Number of traineeships: 4; Prerequisites: M.D. or Ph.D.; Duration: 1-2 years.*

**25. Dr. R. F. Rushmer**
Department of Physiology and Biophysics
University of Washington School of Medicine
Seattle, Washington

Training in modern cardiovascular research techniques, including formal work in mathematics, physics and electronics. *Number of traineeships: 6; Prerequisites: M.D. or Ph.D.; Duration: 2 years.*

**26. Dr. George Sayers**
Department of Physiology
School of Medicine
Western Reserve University
Cleveland 6, Ohio

Research and academic training leading to the Ph.D. degree or associated M.D. training with major emphasis on hemodynamics, celllular physiology and endocrinology. *Number of traineeships: 3; Prerequisites: B.S.; Duration: 4-7 years.*

**27. Drs. B. Schmidt-Nielson, K. Schmidt-Nielson, and K. M. Wilbur**
Department of Zoology
Duke University
Durham, North Carolina

Predoctoral training in cellular and comparative physiology concerning especially water and salt balance and volume regulation. *Number of traineeships: 4; Prerequisites: A.B. or B.S.; Duration: 1-3 years.*

**28. Dr. Maurice B. Visscher**
Department of Physiology
University of Minnesota
Minneapolis 14, Minnesota

Predoctoral training in physiology, including background training in physics and chemistry, with major research opportunities in cardiovascular physiology, broadly defined. *Number of traineeships: 8; Prerequisites: B.S.; Duration: 3-5 years.*

**29. Dr. D. B. Zilversmit**
Department of Physiology
University of Tennessee Medical Center
62 South Dunlap
Memphis 3, Tennessee

Research training in the physiology and biochemistry of lipids, particularly the metabolic and nutritional aspects, including training in techniques of lipid analysis. *Number of traineeships: 3; Prerequisites: M.D. or Ph.D.; Duration: 1-2 years.*

## PUBLIC HEALTH

**30. Dr. Albert V. Hardy**
Director of Research
Florida State Board of Health
Jacksonville, Florida

Graduate research training in Public Health within a State Board of Health, including epidemiology and community aspects of disease. *Number of traineeships: 3; Prerequisites: M.D. or Ph.D.; Duration: 2 or more years.*

**31. Dr. Abraham M. Lilienfeld**
School of Hygiene and Public Health
Johns Hopkins University
Baltimore 5, Maryland

Training in public health aspects of chronic diseases with emphasis on biostatistical, epidemiological, genetic and sociological methods, which may lead to M.P.H. or Dr. P.H. degree. *Number of traineeships: 4; Prerequisites: M.D. or Ph.D.; Duration: 1-2 years.*

**32. Dr. Kirk T. Mosley**
Department of Preventive Medicine and Public Health
University of Oklahoma Medical Center
801 Northeast 13th Street
Oklahoma City 4, Oklahoma

Research training in public health with emphasis on community aspects of disease using sociological, psychological, and epidemiological techniques with emphasis on chronic diseases. *Number of traineeships: 2; Prerequisites: M.D.; Duration: 1-2 years.*

**33. Dr. Robert E. Olson**
Department of Biochemistry and Nutrition
Graduate School of Public Health
University of Pittsburgh
Pittsburgh 13, Pennsylvania

Training in metabolism and nutrition with courses in biochemistry, public health nutrition, biostastistics, epidemiology, and evaluation of nutritional status in man, with emphasis on techniques of clinical investigations. *Number of traineeships: 4; Prerequisites: 1 year internship; Duration: 1-3 years.*

**34. Dr. W. H. Sebrell**
Institute of Nutrition Sciences
School of Public Health
Columbia University
600 West 168th Street
New York 32, New York

Training in nutrition including the social, public health, medical, and biochemical aspects of nutrition with opportunity for clinical research leading to the M.S. or Ph.D. degrees. *Number of traineeships: 1; Prerequisites: B.S. or M.D.; Duration: 1 year.*

**35. Dr. Fredrick J. Stare**
Department of Nutrition
Harvard School of Public Health
One Shattuck Street
Boston 15, Massachusetts

Training in the biochemical and nutritional aspects of atherosclerosis, particularly as related to cholesterol metabolism, using biochemical, clinical and epidemiological research techniques. *Number of traineeships: 7; Prerequisites: B.S.; Duration: 1-3 years.*

# II. CLINICAL DEPARTMENTS

## MEDICINE

**36. Dr. James K. Alexander**
Department of Medicine
Baylor University College of Medicine
Houston 25, Texas

Coordinated clinical and research training with research emphasis on clinical hemodynamics and pulmonary function studies. *Number of traineeships: 1; Prerequisites: M.D.; Duration: 1-2 years.*

**37. Dr. Samuel Bellet**
Division of Cardiology
Philadelphia General Hospital
Philadelphia 4, Pennsylvania

Research training in diagnostic cardiology with emphasis on hemodynamics, and metabolic aspects of heart disease; includes physiologic and biochemical training. *Number of traineeships: 7; Prerequisites: 1 year internship; Duration: 1-2 years.*

**38. Dr. Leonard B. Berman**
Department of Renal Diseases
Research Foundation of Children's Hospital
2125 13th Street, N. W.
Washington, D. C.

Research training in renal diseases and renal physiology. *Number of traineeships: 2; Prerequisites: M.D.; Duration: 2 years.*

**39. Dr. Edward F. Bland**
Department of Medicine
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Combined clinical and research training with research emphasis on hemodynamic and metabolic

aspects of clinical heart disease. *Number of traineeships: 4; Prerequisites: M.D.; Duration: 1-2 years.*

**40. Dr. S. Gilbert Blount**
Department of Medicine
University of Colorado Medical Center
Denver 20, Colorado

Coordinated clinical and research training with emphasis on hemodynamic and pulmonary studies, medical and cardiac surgical aspects, and diagnostic methodology in congenital heart disease. *Number of traineeships: 4; Prerequisites: 2 years residency in medicine; Duration: 2 or more years.*

**41. Dr. Herrman L. Blumgart**
Department of Medicine
Director of Medical Research
Beth Israel Hospital
Boston 15, Massachusetts

Coordinated clinical and research training; research emphasis on mechanisms of heart failure and clinical diagnostic methodologies. *Number of traineeships: 6; Prerequisites: M.D.; Duration: 1-3 years.*

**42. Dr. George E. Burch**
Department of Medicine
Tulane University
1430 Tulane Avenue
New Orleans 23, Louisiana

Research training in inter-related laboratories of vectoreardiography, peripheral vascular and tropical physiology, hemodynamics, and biologic instrumentation in relationship with College of Electrical Engineering. *Number of traineeships: 2; Prerequisites: M.D. or Ph.D.; Duration: 1-5 years.*

**43. Dr. Carleton B. Chapman**
Department of Medicine
University of Texas
Southwestern Medical School
Harry Hines Boulevard
Dallas 35, Texas

Research training in basic cardiopulmonary physiology with emphasis on human exercise problems using catheterization, cineangiocardiographic and other techniques; courses in mathematics, biophysics, electronics. *Number of traineeships: 5; Prerequisites: M.D. or Ph.D.; Duration: 1-2 years.*

**44. Dr. Ernest Craige**
Department of Medicine
University of North Carolina
Chapel Hill, North Carolina

Combined clinical and research training with emphasis on the relationship of physiological events to phonocardiography at catheterization and experimentally. *Number of traineeships: 2; Prerequisites: residency in medicine; Duration: 1-2 years.*

**45. Dr. Lewis Dexter**
Department of Medicine
Harvard Medical School
Peter Bent Brigham Hospital
Boston 15, Massachusetts

Research training opportunities in four relatively independent laboratories: (1) cardiac hemodynamics (Dr. Dexter), (2) cardiac metabolism (Dr. Gorlin), (3) electrocardiography (Dr. H. Levine), and (4) cardiopulmonary dynamics (Dr. Wells). *Number of traineeships: 10; Prerequisites: 1 year medical internship; Duration: 1-3 years.*

**46. Dr. E. Grey Dimond**
Department of Medicine
University of Kansas Medical Center
Kansas City 12, Kansas

Coordinated clinical and research training with research emphasis on clinical diagnostic methodology and hemodynamics; opportunities for more basic cardiac physiology and biochemistry training. *Number of traineeships: 2; Prerequisites: 1 year residency in medicine, surgery or pediatrics; Duration: 2 years.*

**47. Dr. Richard V. Ebert**
Department of Medicine
University of Arkansas Medical Center
Little Rock, Arkansas

Research training in cardio-pulmonary disease including background work in physiology and biochemistry with research interests in pulmonary emphysema and aging changes in the lungs. *Number of traineeships: 3; Prerequisites: 1 year residency in medicine; Duration: 2 years.*

**48. Dr. Howard A. Eder**
Department of Medicine
Albert Einstein College of Medicine of Yeshiva University
Eastchester Road and Morris Park Avenue
New York 61, New York

Research training in biochemistry, especially in lipid metabolism as related to atherosclerosis, and its application to clinical medicine. *Number of traineeships: 2; Prerequisites: M.D. or Ph.D.; Duration: 2 or more years.*

**49. Dr. Laurence B. Ellis**
Thorndike Memorial Laboratory
(Heart Station)
Boston City Hospital
Boston 18, Massachusetts

Combined clinical and research training with research emphasis on hemodynamic studies and diag-

nostic methodology. *Number of traineeships: 2; Prerequisites: 1 year residency in medicine; Duration: 1-2 years.*

**50. Dr. Stuart C. Finch**
Department of Internal Medicine
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut

Training in clinical and investigative hematology with opportunities for independent research experience. *Number of traineeships: 2; Prerequisites: M.D.; Duration: 1-2 years.*

**51. Dr. Charles K. Friedberg**
The Mount Sinai Hospital
1 East 100th Street
New York 29, New York

Research training with investigative emphasis on clinical diagnostic methodology including electrocardiography, catheterization, mechanisms of heart failure, and cardiac surgical problems. *Number of traineeships: 6; Prerequisites: 2 years of residency; Duration: 1-3 years.*

**52. Dr. Robert H. Furman**
Oklahoma University Medical School
Oklahoma Medical Research Foundation
Oklahoma City 4, Oklahoma

Research training in nutritional and endocrine aspects of atherosclerosis and lipid metabolism, with opportunities for further relevant biochemical and clinical training. *Number of traineeships: 2; Prerequisites: B.S., M.D. or Ph.D.; Duration; 1-4 years.*

**53. Dr. Grace A. Goldsmith**
Department of Medicine
Tulane University School of Medicine
1430 Tulane Avenue
New Orleans 12, Louisiana

Training in clinical nutrition, especially biochemical techniques in nutritional diagnosis and research including radioactive isotopes, enzyme chemistry and research in lipid metabolism. *Number of traineeships: 5; Prerequisites: M.D.; Duration: 1-3 years.*

**54. Dr. Tinsley R. Harrison**
Department of Medicine
Medical College of Alabama
Birmingham, Alabama

Clinical research training with research emphasis on diagnostic clinical methods, hemodynamics and cardiac ballistics; informal affiliation with preclinical laboratories. *Number of traineeships: 4; Prerequisites: residency in medicine; Duration: 1-2 years.*

**55. Dr. W. Proctor Harvey**
Division of Cardiology
Department of Medicine
Georgetown University Medical Center
3800 Reservoir Road, N. W.
Washington 7, D. C.

Research training in clinical cardiology with an informal alliance with preclinical departments offering work on correlated basic problems. *Number of traineeships: 4; Prerequisites: completion of medical residency; Duration: 2 years.*

**56. Dr. Hans H. Hecht**
Department of Medicine
University of Utah
Salt Lake City, Utah

Integrated research training in pulmonary, electrophysiologic, hemodynamic and other clinical investigative fields; special courses in mathematics, biophysics, and electronic design. *Number of traineeships: 4; Prerequisites: M.D. or Ph.D.; Duration: 2 years.*

**57. Dr. John B. Hickam**
Department of Medicine
Indiana University Medical School
1100 West Michigan Street
Indianapolis 7, Indiana

Training in the method and techniques of cardiovascular and cardiopulmonary research including basic grounding in mathematics and electronics. *Number of traineeships: 8; Prerequisites: 1 year of residency; Duration: 2 years.*

**58. Dr. Louis N. Katz**
Michael Reese Hospital
Chicago 16, Illinois

Integrated clinical cardiologic and research training with research emphasis on cardiovascular physiology, experimental atherosclerosis, electrocardiography, and experimental and clinical hemodynamics. *Number of traineeships: 12; Prerequisites: internship or residency in internal medicine or Ph.D.; Duration: 1-3 years.*

**59. Dr. Calvin F. Kay**
Department of Medicine
University of Pennsylvania
3400 Spruce Street
Philadelphia 4, Pennsylvania

Research training and related clinical opportunities in laboratories studying myocardial metabolism, hypertension, electrophysiology, hemodynamics, and experimental coronary disease. *Number of traineeships: 7; Prerequisites: 2 years residency; Duration: 1-3 years.*

**60. Dr. Walter M. Kirkendall**
Department of Medicine
State University of Iowa
General Hospital
Iowa City, Iowa

Training in a research unit within the Department of Medicine consisting of renal and electrolyte, hemodynamic, arteriosclerosis and pulmonary function laboratories; emphasis on clinical research problems. *Number of traineeships: 4; Prerequisites: 1-3 years medical residency; Duration: 2 years.*

**61. Dr. Charles E. Kossmann**
Lenox Hill Hospital
111 East 76th Street
New York 21, New York

Coordinated clinical and research training, with research emphasis on electrophysiology; opportunities for more basic biophysical training. *Number of traineeships: 2; Prerequisites: 2 years residency in medicine; Duration: 2 years.*

**62. Dr. Charles L. Leedham**
Departments of Research and Internal Medicine
The Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation
2020 East 93rd Street
Cleveland 6, Ohio

Training in the fundamental clinical and laboratory aspects of cardiovascular disease including diagnostic cardiology, renal disease and hypertension, etc. *Number of traineeships: 6; Prerequisites: 3 years residency in medicine; Duraton: 2 years.*

**63. Dr. Aldo A. Luisada**
Division of Cardiology
Chicago Medical School
Chicago 8, Illinois

Combined clinical and research training with research emphasis on hemodynamics, phonocardiography, and experimental cardiopulmonary physiology. *Number of traineeships: 5; Prerequisites: M.D. or Ph.D.; Duration: 1-3 years.*

**64. Dr. Richard H. Lyons**
Department of Medicine
State University of New York,
Upstate Medical Center
150 Marshall Street
Syracuse 10, New York

Research training in pulmonary, electrophysiologic and other areas of cardiovascular disease with opportunity for further training in basic science disciplines. *Number of traineeships: 3; Prerequisites: 2 years residency in medicine; Duration: 1-3 years.*

**65. Dr. Werner Maas**
Department of Medicine
New York University Medical School
Bellevue Medical Center
550 First Avenue
New York, New York

Research training in medical genetics including basic and clinical training appropriate to the research interests of the trainee. *Number of traineeships: 4; Prerequisites: M.D. or Ph.D.; Duration: 3 years.*

**66. Dr. Victor A. McKusick**
Department of Medicine
Johns Hopkins University School of Medicine
Johns Hopkins Hospital
Baltimore 5, Maryland

Advanced training in medical genetics including formal instruction and related research experience with staff from several departments. *Number of traineeships: 10; Prerequisites: B.S., M.D. or Ph.D.; Duration: 1-2 years.*

**67. Dr. C. Thorpe Ray**
Department of Medicine
University of Missouri Medical Center
Columbia, Missouri

Coordinated clinical, physiological, and biophysical research training with emphasis on hemodynamics, pulmonary, physiological and isotopic techniques. *Number of traineeships: 3; Prerequisites: M.S., M.D. or Ph.D.; Duration: 1-3 years.*

**68. Dr. Samuel T. R. Revell, Jr.**
Division of Hypertension
Department of Medicine
University of Maryland School of Medicine
Baltimore 1, Maryland

Research training in renal disease and hypertension, particularly artificial dialysis, serotonin metabolism, renal tissue enzymes, and the effects of various experimental techniques on standard clearances. *Number of traineeships: 2; Prerequisites: 2 years residency in medicine; Duration: 1-2 years.*

**69. Dr. Simon Rodbard**
Chronic Disease Research Institute
University of Buffalo
Buffalo 14, New York

Research training in clinical and experimental cardiac physiology, with opportunities for more advanced training in preclinical departments. *Number of traineeships: 2; Prerequisites: M.D. or Ph.D.; Duration: 1-3 years.*

**70. Dr. George E. Schreiner**
Department of Medicine
Georgetown University Medical Center
Georgetown University Hospital
Washington 7, D. C.

Research training in renal disease including physiology and pathology of the kidney and use of the artificial kidney, with independent research opportunities. *Number of traineeships: 2; Prerequisites: 2 years residency in medicine; Duration: 2 years.*

**71. Dr. William B. Schwartz**
Department of Medicine
Tufts University School of Medicine
New England Center Hospital
171 Harrison Avenue
Boston 11, Massachusetts

Research training in renal and electrolyte physiology and clinical renal disease, particularly renal mechanisms for the control of electrolyte and acid-base equilibrium. *Number of traineeships: 6; Prerequisites: 1 year residency in medicine; Duration: 1 or more years.*

**72. Dr. John R. Smith**
Department of Medicine
Washington University School of Medicine
St. Louis 10, Missouri

Four laboratories offer research training in (1) coagulation and fibrinolysis, (Dr. Sherry); (2) myocardial ultra-structure, (Dr. Smith); (3) hemodynamics, (Dr. Parker); (4) hypertension and renal physiology, (Drs. Perry and Bricker). *Number of traineeships: 10; Prerequisites: M.D. or Ph.D.; Duration: 1-3 years.*

**73. Dr. Maurice Sokolow**
Department of Cardiology
University of California
Medical Center
San Francisco 22, California

Clinical training coordinated with Dr. Comroe's research training program (#127), includes opportunities for training in mathematics, physics, physiology, pharmacology and modern cardiovascular diagnostic techniques. *Number of traineeships: 2; Prerequisites: M.D.; Duration: 2 years.*

**74. Dr. Eugene A. Stead**
Department of Medicine
Duke University School of Medicine
Durham, North Carolina

Coordinated clinical and research training with research emphasis on cardiac and peripheral vascular hemodynamics, sociological aspects of disease, lipid metabolism, renal, and pulmonary disease. *Number of traineeships: 8; Prerequisites: M.D.; Duration: 1-3 years.*

**75. Dr. Mario Stefanini**
Department of Medicine
Tufts University School of Medicine
St. Elizabeth's Hospital
736 Cambridge Street
Boston 35, Massachusetts

Training in hematologic research with emphasis on biochemistry, coagulation and fibrinolysis as related to cardiovascular disorders. *Number of traineeships: 2; Prerequisites: M.D. or Ph.D.; Duration: 2 years.*

**76. Dr. Burton S. Tabakin**
Department of Medicine
University of Vermont
Burlington, Vermont

Training in research techniques in clinical cardiopulmonary physiology. *Number of traineeships: 1; Prerequisites: 1-2 years medical residency; Duration: 1-2 years.*

**77. Dr. David A. Turner**
Biochemistry Research Division
Department of Medicine
Johns Hopkins School of Medicine
Sinai Hospital of Baltimore, Inc.
Baltimore 5, Maryland

Specialized training in newer lipid analytical techniques for those particularly interested in atherosclerosis and aging with special emphasis in vapor phase and silicic acid chromatography and radioisotope techniques. *Number of traineeships: 2; Prerequisites: M.D. or Ph.D.; Duration: 30 days for senior persons; 1-2 years for others.*

**78. Dr. James V. Warren**
Department of Medicine
University of Texas
Medical Branch
Galveston, Texas

Research training with emphasis on integrative mechanisms in heart function, both experimental and clinical, including a close relationship with clinical cardiologic activities. *Number of traineeships: 3; Prerequisites: M.D. or Ph.D.; Duration: 1-3 years.*

**79. Dr. Stewart Wolf**
Department of Medicine
University of Oklahoma School of Medicine
800 N. E. 13th Street
Oklahoma City 4, Oklahoma

Research training in effects of psychological and social forces on cardiovascular phenomena, with experience in psychodynamics. *Number of traineeships: 4; Prerequisites: M.D.; Duration: 1-2 years.*

**80. Dr. J. Edwin Wood**
Department of Internal Medicine
Medical College of Georgia
Augusta, Georgia

Research training in clinical cardiovascular investigation including design and techniques of experimentation, affiliated with Dr. Hamilton's program in cardiac physiology (#120). *Number of traineeships: 3; Prerequisites: M.D. or Ph.D.; Duration: 1-3 years.*

## OBSTETRICS-GYNECOLOGY

**81. Dr. Russell R. de Alvarez**
Department of Obstetrics and Gynecology
University of Washington Hospital
School of Medicine
Seattle 5, Washington

Training for academic and research careers in obstetrics and gynecology with special emphasis on the methodology and techniques of basic and clinical investigation and in toxemia of pregnancy. *Number of traineeships: 2; Prerequisites: B.S. in chemistry or M.D.; Duration: 1-2 years.*

**82. Dr. N. S. Assali**
Department of Obstetrics and Gynecology
University of California Medical Center
Los Angeles 24, California

Research training in circulatory and physiological problems related to obstetrics, with emphasis on the fetal, placental, and biochemical aspects. *Number of traineeships: 2; Prerequisites: M.D.; Duration: 1-2 years.*

**83. Dr. Edith L. Potter**
Department of Obstetrics and Gynecology
Chicago Lying-in Hospital
University of Chicago
Chicago 37, Illinois

Research training in the pathology and physiology of the fetus and newborn in relation to perinatal mortality, to prepare career investigators. *Number of traineeships: 2; Prerequisites: M.D.; Duration: 1-2 years.*

**84. Dr. Seymour L. Romney**
Department of Obstetrics and Gynecology
Albert Einstein College of Medicine of Yeshiva University
Eastchester Road and Morris Park Avenue
New York 61, New York

Postdoctoral research training particularly concerned with maternal and fetal cardiovascular adaptations of pregnancy, including neonatal respiratory problems. *Number of traineeships: 3; Prerequisites: Ph.D. or M.D.; Duration: 1 or more years.*

## PEDIATRICS

**85. Dr. Henry L. Barnett**
Department of Pediatrics
Albert Einstein College of Medicine of Yeshiva University
Eastchester Road and Morris Park Avenue
New York 61, New York

Research training in pediatrics concerning particularly the influence of growth on the renal and endocrine control of water and electrolyte metabolism. *Number of traineeships: 3; Prerequisites: M.D. or Ph.D.; Duration: 2-3 years.*

**86. Dr. Sidney Blumenthal**
Department of Pediatrics
Columbia University College of Physicians and Surgeons
630 West 168th Street
New York 32, New York

Training in pediatric cardiology with opportunities for independent investigation as well as special clinical activities. *Number of traineeships: 4; Prerequisites: completion of pediatric residency; Duration: 2 years.*

**87. Dr. Louis K. Diamond**
Department of Pediatrics
Harvard Medical School
Children's Medical Center
300 Longwood Avenue
Boston, Massachusetts

Research training in the hematology and physiology of the hematopoietic and circulatory systems in infancy and childhood. *Number of traineeships: 4; Prerequisites: completion of pediatric residency; Duration: 1-2 years.*

**88. Dr. James N. Etteldorf**
Department of Pediatrics
University of Tennessee College of Medicine
62 South Dunlap
Memphis 3, Tennessee

Training in pediatric cardiology with research emphasis on hemodynamics, renal disease, metabolism, etc.; close affiliation with preclinical departments for additional training. *Number of traineeships: 3; Prerequisites: completion of pediatric residency; Duration: 1-3 years.*

**89. Dr. Donald C. Fyler**
Department of Pediatrics
Children's Hospital of Los Angeles
4614 Sunset Boulevard
Los Angeles 27, California

Training in pediatric cardiology with research emphasis on related basic physiology. *Number of traineeships: 3; Prerequisites: completion of resi-*

*dency in pediatrics or medicine; Duration: 1-3 years.*

**90. Dr. Jerome S. Harris**
Department of Pediatrics
Duke University School of Medicine
Durham, North Carolina

Training in pediatric cardiovascular research, including diagnostic methodology (catheterization, dye dilution methods, etc.), radio isotopes, and surgical and physiological research techniques. *Number of traineeships: 2; Prerequisites: residency in pediatrics; Duration: 1-2 years.*

**91. Dr. Doris A. Howell**
Department of Pediatrics
Duke University School of Medicine
Durham, North Carolina

Research training in the hematologic diseases of children with particular reference to anemias, blood immunology and banking, coagulation defects, and use of radioactive isotopes and chemotherapeutic agents. *Number of traineeships: 3; Prerequisites: 2 years of pediatric training; Duration: 1-2 years.*

**92. Dr. Samuel Kaplan**
Department of Pediatrics
College of Medicine
University of Cincinnati
Cincinnati 29, Ohio

Training in pediatric cardiology; research emphasis on diagnostic methods and congenital cardiovascular diseases. *Number of traineeships: 2; Prerequisites: M.D. or Ph.D.; Duration: 2-3 years.*

**93. Dr. Edward C. Lambert**
Department of Pediatrics
University of Buffalo School of Medicine
219 Bryant Street
Buffalo 22, New York

Training in pediatric cardiology, research emphasis on diagnostic methodology with informal affiliation with preclinical departments. *Number of traineeships: 2; Prerequisites: residency in pediatrics; Duration: 1-2 years.*

**94. Dr. Alexander S. Nadas**
Department of Pediatrics
Harvard Medical School
Children's Medical Center
300 Longwood Avenue
Boston, Massachusetts

Training in pediatric cardiology particularly congenital heart disease and rheumatic fever, with clinical and physiologic research in hemodynamics, pulmonary hypertension, phonocardiography, electrocardiography. *Number of traineeships: 9; Prerequisites: residency in pediatrics or medicine; Duration: 2 years.*

**95. Dr. Nathan B. Talbot**
Children's Medical Service
Massachusetts General Hospital
Boston 14, Massachusetts

Research training in pediatrics, particularly in the fundamentals of metabolism and endocrinology as related to the regulation of body water, electrolytes and protein homeostasis. *Number of traineeships: 4; Prerequisites: M.D.; Duration: 1-2 years.*

**96. Dr. Helen B. Taussig**
Department of Pediatrics
Cardiac Clinic, Harriet Lane Home
Johns Hopkins Hospital
Baltimore 5, Maryland

Training in pediatric cardiology with special emphasis on diagnostic methodology and management of congenital cardiac malformations. *Number of traineeships: 8; Prerequisites: 1 year of pediatric residency or 1 year of medicine and cardiology; Duration: 1-2 years.*

## CLINICAL THERAPEUTICS

**97. Dr. Samuel Bellet**
Division of Cardiology
Philadelphia General Hospital
34th St. & Curie Avenue
Philadelphia 4, Pennsylvania

Research training in a diversified cardiovascular research laboratory, with emphasis on cardio-active agents; biostatistics and relevant basic science training in other departments. *Number of traineeships: 3; Prerequisites: 1 year internship; Duration: 2-3 years.*

**98. Dr. Frank A. Howard**
Harvard University
Lemuel Shattuck Hospital
170 Morton Street
Jamaica Plains 30, Massachusetts

Multidepartmental program with special biostastisties and pharmacodynamics training; basic research in drug action in the clinical department of the trainee's choice. *Number of traineeships: 3; Prerequisites: M.D. and 2 years of clinical training; Duration: 1-3 years.*

**99. Dr. Louis Lasagna**
Clinical Pharmacology Section
Department of Medicine
Johns Hopkins Hospital
Baltimore 5, Maryland

Joint training between departments of medicine and pharmacology with special training in statistics and pharmacodynamics; basic research relevant to drug action in clinical department of trainee's choice. *Number of traineeships: 3; Prerequisites: M.D.; Duration: 2-3 years.*

## RADIOLOGY

**100. Dr. Russell H. Morgan**
Department of Radiology
The Johns Hopkins Hospital
Johns Hopkins University
Baltimore 5, Maryland

Research training for postdoctoral candidates in the techniques and applications of cardiac radiology integrated with the research and clinical activities of other departments. *Number of traineeships: 2; Prerequisites: completion of internship; Duration: 1-2 years.*

**101. Dr. Charles M. Nice, Jr.**
Department of Radiology
Tulane University School of Medicine
1430 Tulane Avenue
New Orleans, Louisiana

Training roentgenologists in specialized aspects of research and diagnosis in cardiovascular roentgenology. *Number of traineeships: 1; Prerequisites: three years of residency in Radiology; Duration: 1 or more years.*

## SURGERY

**102. Dr. Ivan D. Baronofsky**
Department of Surgery
The Mount Sinai Hospital
Fifth Avenue and One Hundredth Street
New York 29, New York

Training in cardiovascular surgery and research, clinically, and in the experimental surgery laboratory. *Number of traineeships: 3; Prerequisites: completion of general surgery residency; Duration: 3-4 years.*

**103. Dr. H. H. Bradshaw**
Department of Surgery
Bowman Gray School of Medicine
South Hawthorne Road
Winston Salem, North Carolina

Training in the experimental approach to clinical and basic cardiovascular problems. *Number of traineeships: 1; Prerequisites: completion of residency in general and thoracic surgery; Duration: 1 year.*

**104. Dr. Oscar Creech, Jr.**
Department of Surgery
Tulane University School of Medicine
1430 Tulane Avenue
New Orleans, Louisiana

Training in techniques of investigation in cardiovascular surgery, including pulmonary function and extra-corporeal circulation techniques. *Number of traineeships: 4; Prerequisites: surgical residency training; Duration: 1-2 years.*

**105. Drs. J. Frances Dammann, Jr. and William H. Muller, Jr.**
Department of Surgery
University of Virginia Hospital
Charlottesville, Virginia

Training in surgical cardiology to improve total understanding of the physiologic, pathologic, diagnostic and therapeutic approach to cardiovascular diseases amenable to surgical treatment. *Number of traineeships: 4; Prerequisites: 1 year residency in medicine, surgery or pediatrics; Duration: 2 years.*

**106. Dr. Michael E. DeBakey**
Department of Surgery
Baylor University College of Medicine
Houston 25, Texas

Research training in cardiac, arterial and peripheral vascular surgery; affiliated with basic science departments. *Number of traineeships: 8; Prerequisites: completion of general surgery residency; Duration: 1-2 years.*

**107. Dr. Jacob Fine**
Department of Surgery
Beth Israel Hospital
330 Brookline Avenue
Boston 15, Massachusetts

Training in surgical cardiovascular research with emphasis on factors related to peripheral vascular collapse and related peripheral circulatory problems. *Number of traineeships: 3; Prerequisites: M.D. or Ph.D.; Duration: 1 year.*

**108. Dr. Frank Gerbode**
Department of Cardiovascular Surgery
San Francisco - Stanford Hospital
San Francisco 15, California—and the
Stanford Medical Center
Palo Alto, California

Training in basic and clinical cardiovascular surgery, including rotation through laboratories for cardiac catheterization, pulmonary function, angiocardiography and the experimental animal laboratory. *Number of traineeships: 3; Prerequisites: residency in surgery, thoracic surgery, medicine or pediatrics; Duration: 1-4 years.*

**109. Dr. John H. Gibbon, Jr.**
Department of Surgery
Jefferson Medical College
1025 Walnut Street
Philadelphia 7, Pennsylvania

Clinical and experimental surgical training with research emphasis on cardio-respiratory physiology and cardiac by-pass methods. *Number of traineeships: 2; Prerequisites: completion of surgery residency; Duration: 1 year.*

**110. Dr. Henry Haimovici**
Surgical Division
Montefiore Hospital
New York 67, New York

Training in the physiology and surgery of vascular disease, including research education in the basic aspects of peripheral vascular disease. *Number of traineeships: 1; Prerequisites: residency in surgery; Duration: 1-2 years.*

**111. Dr. C. Rollins Hanlon**
Department of Surgery
St. Louis University
1325 South Grand
St. Louis, Missouri

Training in clinical and basic research in cardiovascular surgery, with relevant operative experience. *Number of traineeships: 1; Prerequisites: surgical residency; Duration: 1-4 years.*

**112. Dr. Claude R. Hitchcock**
Surgery Department
Minneapolis General Hospital
Minneapolis 15, Minnesota

Combined clinical and research training in cardiovascular surgical techniques. *Number of traineeships: 3; Prerequisites: completion of surgery residency; Duration: 1 year.*

**113. Dr. James V. Maloney, Jr.**
Department of Surgery
University of California Medical Center
Los Angeles 24, California

Training in cardiovascular surgery with emphasis on the basic biochemical and physiologic aspects. *Number of traineeships: 4; Prerequisites: M.D.; Duration: 1-3 years.*

**114. Dr. K. Alvin Merendino**
Department of Surgery
University of Washington
School of Medicine
Seattle 5, Washington

Surgical research training with opportunities for collaborative training with cardiology, radiology, pharmacology and pathology. *Number of traineeships: 2; Prerequisites: surgical residency; Duration: 1-2 years.*

**115. Drs. Francis D. Moore and Dwight E. Harken**
Harvard Medical School
Department of Surgery
Peter Bent Brigham Hospital
721 Huntington Avenue
Boston 15, Massachusetts

Training in cardiovascular research concepts and techniques, with emphasis on physiologic, biochemical, metabolic and clinical investigation. *Number of traineeships: 2; Prerequisites: M.D.; Duration: 1-2 years.*

**116. Dr. Will C. Sealy**
Department of Surgery
Duke Medical Center
Durham, North Carolina

Training in cardiovascular surgery and research, including congenital and valvular heart disease, coronary artery disease, peripheral vascular disease, and the autonomic nervous system. *Number of traineeships: 5; Prerequisites: M.D.; Duration: 1 year.*

**117. Dr. Harry B. Shumacker**
Department of Surgery
Indiana University Medical Center
1100 West Michigan Street
Indianapolis 7, Indiana

Training in basic and experimental cardiovascular surgery. *Number of traineeships: 3; Prerequisites: internship; Duration: 1-3 years.*

**118. Dr. Henry Swan**
Department of Surgery
University of Colorado School of Medicine
4200 East Ninth Avenue
Denver 20, Colorado

Research training in experimental cardiovascular techniques, with formal instructions in biochemical and physiological techniques and other basic sciences. *Number of traineeships: 4; Prerequisites: M.D.; Duration: 1 year.*

**119. Dr. Richard Warren**
Surgical Department
Peter Bent Brigham Hospital
721 Huntington Avenue
Boston 15, Massachusetts

Research training in vascular surgery, with germane clinical and teaching opportunities, including investigation of blood flow in the extremities and blood coagulation. *Number of traineeships: 1; Prerequisites: 3 years residency in surgery; Duration: 1 year.*

## III. MULTIDEPARTMENTAL

### PRECLINICAL

**120. Drs. W. F. Hamilton and R. P. Ahlquist**
Department of Physiology & Pharmacology
Medical College of Georgia
Augusta, Georgia

Training in techniques of basic cardiovascular research with emphasis on supervised research on a

problem of the candidate's choice, leading to publishable contributions to the literature. *Number of traineeships: 4; Prerequisites: M.D., Ph.D., or 2 years of experience in research; Duration: 1-2 years.*

## CLINICAL

**121. Dr. Robert H. Bayley**
Department of Medicine
University of Oklahoma
School of Medicine
Oklahoma City 4, Oklahoma

Research training in cardiovascular disease with emphasis in cardiac potentials, hemodynamics, theromistic and radioisotope techniques, and immunology as related to heart disease. *Number of traineeships: 2; Prerequisites: M.D., M.S. or Ph.D.; Duration: 2 years.*

**122. Dr. John T. Cuttino**
Department of Surgery
Medical College of South Carolina
16 Lucas Street
Charleston, South Carolina

Research and related clinical training in medical cardiology and cardiovascular surgery. *Number of traineeships: 3; Prerequisites: 1 year surgery residency; Duration: 1 year.*

**123. Dr. Allan V. N. Goodyer**
Department of Medicine
Yale University School of Medicine
New Haven, Connecticut

Integrated cardiovascular research training in the departments of medicine, surgery, pediatrics and radiology, including related biostatistical training. *Number of traineeships: 4; Prerequisites: M.D.; Duration: 2 years.*

## CLINICAL-PRECLINICAL

**124. Dr. E. Cowles Andrus**
Joint Committee on Cardiovascular
Teaching and Research
Johns Hopkins University
School of Medicine
Baltimore 5, Maryland

Research training in a number of independent laboratories with different cardiovascular research interests in both preclinical and clinical departments. *Number of traineeships: 15; Prerequisites: M.D. or Ph.D.; Duration: 2 or more years.*

**125. Dr. Robert A. Bruce**
Division of Cardiology
Department of Medicine
University of Washington
Seattle, Washington

Research training in cardiovascular fields; first year in basic science laboratories (anatomy, physiology, pharmacology, pathology, microbiology); second year in clinical laboratories (medicine, pediatrics, radiology and surgery) according to candidates' interests. *Number of traineeships: 4; Prerequisites: M.D. or Ph.D.; Duration: 2 or more years.*

**126. Dr. H. Mead Cavert**
1360 Mayo Memorial
College of Medical Sciences
University of Minnesota
Minneapolis 14, Minnesota

Research training in the general area of cardiovascular disease in several preclinical and clinical departments. *Number of traineeships: 15; Prerequisites: 1 or more years of residency or Ph.D.; Duration: 1-3 years.*

**127. Dr. Julius H. Comroe, Jr.**
Cardiovascular Research Institute
University of California Medical Center
San Francisco 22, California

Basic and clinical cardiovascular-pulmonary research with multidepartmental staff; special seminars in mathematics, physics, physical chemistry, statistics, and integrated basic medical sciences. *Number of traineeships: 4; Prerequisites: B.S. or M.D.; Duration: 1-2 years.*

**128. Dr. Charles W. Crumpton**
Cardiovascular Research Laboratory
University of Wisconsin
1300 University Avenue
Madison 6, Wisconsin

Cardiovascular research training involving various basic and clinical departments oriented towards the trainees' interests. *Number of traineeships: 5; Prerequisites: B.S., M.S. or M.D. with 2 years of clinical residency; Duration: 1-3 years.*

**129. Dr. James W. Dow**
Circulation Laboratory
Presbyterian Hospital
51 North 39th Street
Philadelphia 4, Pennsylvania

Interdisciplinary research training, including course work at the Drexel Institute of Technology, for both physical and biological scientists, stressing the application of physical and engineering sciences to the human system. *Number of traineeships: 12; Prerequisites: Physical scientist—B.S. in engineering, physics, or mathematics; Biological scientist—B.S. in biology or physiology, or M.D.; Duration: 2 or more years.*

**130. Dr. F. Lowell Dunn**
Department of Internal Medicine
University of Nebraska
College of Medicine
Omaha, Nebraska

Training coordinated with College of Engineering, offering medical electronics and biophysics to M.D.'s and biology and physiology to electrical engineers. *Number of traineeships: 8; Prerequisites: B.S. or M.D.; Duration: 1-3 years.*

**131. Dr. David P. Earle**
Department of Medicine
Northwestern University Medical School
303 East Chicago Avenue
Chicago 11, Illinois

Research and academic training in the cardiovascular field using appropriate disciplines reflecting the interests of the trainee, including one or two years for independent research. *Number of traineeships: 4; Prerequisites: Completion of residency or Ph.D.; Duration: 4-5 years.*

**132. Dr. John M. Evans**
Department of Medicine
George Washington University
School of Medicine
Washington, D. C.

Research training in hemodynamics, renal and electrolyte metabolism, electrocardiography, lipid metabolism, angiocardiography, etc., in departments of Medicine, Physiology, and Biochemistry, including basic science training. *Number of traineeships: 2; Prerequisites: 2 years of residency; Duration: 2-5 years.*

**133. Dr. Paul F. Formel**
Department of Medicine
Albany Medical College
Albany, New York

Research training coordinated between preclinical and clinical departments in the cardiovascular field of the trainee's choice. *Number of traineeships: 3; Prerequisites: M.D. or Ph.D.; Duration: 2 years.*

**134. Dr. Harold D. Green**
Department of Physiology and Pharmacology
Bowman Gray School of Medicine
Winston-Salem, North Carolina

Coordinated training of cardiovascular investigators in both basic and clinical fields involving chiefly the Departments of Physiology and Pharmacology, Medicine, Surgery, and Radiology. *Number of traineeships: 10; Prerequisites: B.A., Ph.D. or M.D.; Duration: 1-3 years.*

**135. Dr. W. E. Macpherson**
Department of Physiology
School of Medicine
College of Medical Evangelists
Loma Linda, California

Training in basic research techniques primarily in the cardiopulmonary field with major concentration in the departments of physiology and medicine. *Number of traineeships: 1; Prerequisites: M.D. or Ph.D.; Duration: 1 year.*

**136. Dr. Samuel Proger**
Department of Medicine
New England Center Hospital
171 Harrison Avenue
Boston, Massachusetts

Cooperative research training between the Massachusetts Institute of Technology and New England Center Hospital combining physical sciences, molecular biology, and clinical investigation. *Number of traineeships: 6; Prerequisites: M.D.; Duration: 3 years.*

**137. Dr. Arthur P. Richardson**
Emory University School of Medicine
Emory University
Atlanta 22, Georgia

Coordinated research training in cardiovascular disease involving particularly the departments of pharmacology, physiology, and medicine. *Number of traineeships: 10; Prerequisites: M.D. or Ph.D.; Duration: 1 or more years.*

**138. Dr. Roger Warren Sevy**
Department of Pharmacology
Temple University School of Medicine
3400 N. Broad Street
Philadelphia 40, Pennsylvania

Research training in cardiovascular physiology and disease in the departments of pharmacology, physiology, medicine, and radiology emphasizing methodology and experimental design. *Number of traineeships: 6; Prerequisites: B.S., M.S., Ph.D. or M.D.; Duration: 1-4 years.*

**139. Dr. Robert W. Wilkins**
Department of Medicine
Boston University School of Medicine
65 East Newton Street
Boston 18, Massachusetts

Multidisciplinary training in cardiovascular research, including pharmacology, physiology, biochemistry, surgery, medicine, and clinical investigation. *Number of traineeships: 7; Prerequisites: B.S., M.D. or Ph.D.; Duration: 1-3 or more years.*

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